FUNCTIONAL NEUROIMAGING OF THE INTERACTION BETWEEN SOCIAL AND EXECUTIVE NEURAL CIRCUITRY IN INDIVIDUALS WITH HIGH-FUNCTIONING AUTISM

Kimberly Lynn Hills Carpenter

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Curriculum in Neurobiology

Chapel Hill
2011

Approved By:

Dr. Aysenil Belger

Dr. Jim Bodfish

Dr. Gabriel Dichter

Dr. Kevin LaBar

Dr. Joseph Piven

Dr. Aldo Rustioni

ABSTRACT

KIMBERLY LYNN HILLS CARPENTER: Functional Neuroimaging of the Interaction between Social and Executive Neural Circuitry in Individuals with High-Functioning Autism
(Under the direction of Aysenil Belger)

Autism has been associated with deficits in both social cognition and aspects of executive processing. While previous studies have elegantly demonstrated deifficts in each of these processes in isolation, little is known about the interaction between these cognitive domains. The goal of this research was twofold: aim one was to utilize functional magnetic resonance imaging (fMRI) technology to probe how the neurotypical brain resolves competition between task-irrelevant social-cues and goal-directed information during an executive task in which the social context is irrelevant to the executive component. Aim two was to utilize the same fMRI task to probe the interaction between the social-cue and executive networks in a group of individuals with high-functioning autism. Elucidating the neural underpinnings of how individuals with autism differentially resolve competition between social-cues and executive attention may provide insight into the neural circuitry underlying the increased difficulty that individuals with autism often exhibit when performing executive tasks administered in a social context and more broadly expands our understanding of the social cognitive deficits in autism.

Results from this work suggest that the presence of task-irrelevant social cues, namely pictures of eyes, increased attention to the target stimulus in both neurotypical controls and individuals with autism. Specifically, behavioral results suggest that in neurotypical participants the social cue facilitated target detection and promoted discrimination between target and non-target events. In contrast, while social cues behaviorally facilitated target detection in individuals with autism, the social information simultaneously impaired their ability to discriminate between target and non-target events. The enhanced discrimination of target and non-target events in neurotypical controls is likely due to the engagement of frontal cognitive control and selective attention circuitry, which modulates attention to and enhances processing of task-relevant information while filtering distracting irrelevant sensory input. Conversely, dysregulation of fronto-limbic circuits in individuals with autism was associated with an inability to filter interference by the task-irrelevant social stimuli, thus resulting in reduced executive control processes and decreased ability to discriminate between stimuli paired with task-irrelevant eyes.

DEDICATION

To my parents, you have always pushed me to do my very best and have told me since the day I was born that I could achieve anything I set my mind to. I am the person I am because of your love, support, and unwavering confidence in me. I love you both.

To my wonderful husband, I will be forever grateful to you for the sacrifices that you have made so that I can achieve my dreams. You have been there for me through the ups and downs and have never once waivered in your support for me. I love you with all of my heart and cannot imagine sharing this journey with anyone except you.

To Trey, Sherry, and the rest of the Peterson family, you opened your house and your lives to me and in the process introduced me to the amazing world of autism. You are my inspiration.

ACKNOWLEDGEMENTS

I would like to express my immense gratitude to my advisor, Dr. Aysenil Belger, for allowing me the freedom to explore my own research interests while providing me with unparalleled support and guidance. I would also like to thank my clinical co-mentor, Dr. Joseph Piven, for his guidance and his commitment to my training in the clinical aspects of autism spectrum disorders. Additionally, I would like to express my gratitude to my undergraduate research mentor, Dr. Julian Keith, without whom I would have never discovered my love for neuroscience. A much-deserved thank you also goes to Drs. Gabriel Dichter and Sarah Hart, as well as Joshua Bizzell, all of whom have provided me with an incredible amount of support and hours of training throughout the years. Furthermore, special thanks are extended to the additional members of my committee, Drs. Aldo Rustioni, Kevin LaBar, and Jim Bodfish, for their time, knowledge, and guidance throughout the development of this research project. Additionally, I would like to thank the Curriculum in Neurobiology and the Program in Translational Medicine for providing me with an exceptional training environment and financial support. Special thanks also go to Morgan Parlier, Deanna Tracy, Corrie Walston, and Renee Clark for their help with recruitment and collection of clinical data. I would also like to extend my most heartfelt gratitude to the participants and their families, many of whom traveled hundreds of miles to contribute to this research project. Finally, to the friends I have

had the great fortune to make while in graduate school, thank you for going on this amazing adventure with me. I could never have picked a better group of people to surround myself with and I could not have done this without your love and support.

This research would not have been possible without funding from an NIH Predoctoral Training Grant (T32 NS007431), the Howard Hughes Medical Institute Program in Translational Medicine, Autism Speaks Predoctoral Training Fellowship Grant # 5-40643, and the Royster Society of Fellows - Carol and Edward Smithwick Dissertation Fellowship. Additional research support was supplied by NIMH Grants HD40127 and U54MH66418, the NC TraCS Institute Research Funding – National Center for Research Resources Award # UL1RR025747, and the UNC University Research Council Small Grants Program.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAL	Automated Anatomical Labeling
ACC	Anterior Cingulate Cortex
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
AI	Anterior Insula
aMTG	Anterior Middle Temporal Gyrus
BA	Brodmann Area
BET	Brain Extraction Tool
BIAC	Brain Imaging and Analysis Center
BOLD	Brain Oxygen Level Dependent
BSR	Bootstrap Ratio
dACC	Dorsal Anterior Cingulate Cortex
DECS	Dorsal Executive Control System
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
EEG	Electroencephalography
ERP	Event Related Potential
FEAT	FMRI Expert Analysis Tool
FEF	Frontal Eye Fields
FFA	Fusiform Face Area
FFC	Fusiform Cortex

FLIRT	FMRIB's Linear Image Registration Tool
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FOV	Field of View
FSL	FMRIB Software Library
FWHM	Full-Width Half-Maximum
GLM	General Linear Model
GRF	Gaussian Random Field
HDR	Hemodynamic Response Curve
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IPL	Inferior Parietal Lobule
IPS	Intraparietal Sulcus
ITG	Inferior Temporal Gyrus
LV	Latent Variable
MDN	Medial Dorsal Nucleus
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MTG	Middle Temporal Gyrus
OFA	Occipital Face Area
OFC	Orbital Frontal Cortex

PCA	Principal Components Analysis
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
pITG	Posterior Inferior Temporal Gyrus
PLS	Partial Least Squares
pMTG	Posterior Middle Temporal Gyrus
PPI	Psychophysiological Interaction
rACC	Rostral Anterior Cingulate Cortex
ROI	Region of Interest
RT	Reaction Time
SFG	Superior Frontal Gyrus
SMG	Supramarginal Gyrus
ST-PLS	Spatiotemporal Partial Least Squares
STS	Superior Temporal Sulcus
TE	Echo Delay Time
TI	Inversion Time
TOM	Theory of Mind
TPJ	Temporal Parietal Junction
TR	Repetition Time
vACC	Ventral Anterior Cingulate Cortex
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex

VSAPS Ventral Social-Affective Processing System

WASI Weshler Abbreviated Scales of Intelligence

WCST Wisconsin Card Sorting Task

CHAPTER 1. INTRODUCTION

AUTHOR'S NOTE: Excerpts of this work have contributed to publications in the Journal of Neurodevelopmental Disorders (use permission license #2617681162108) and the Journal of Neurotoxicity Research (use permission license #2617680902955) under the titles:

> The Benefit of Directly Comparing Autism and Schizophrenia to Reveal Mechanisms of Social Cognitive Impairment. Sasson, N. J., Pinkham, A. E., Carpenter, K.L.H., Belger, A. (in press), Journal of Neurodevelopmental Disorders.
>
> The Neural Circuitry of Autism. Belger, A., Carpenter, K.L.H., Yucel, G.H., Cleary, K.M., Donkers, F.C. (in press), Journal of Neurotoxicity Research.

The ability to vary behavior in response to a changing environment or to inhibit interference from competing or distracting information while promoting goal-directed behavior is crucial for adaptive functioning. These abilities require complex neurocognitive processes, including response preparation, suppression of interference by competing stimuli, and inhibition of prepotent responses, which are collectively referred to as cognitive control (MacDonald et al., 2000). Cognitive control is commonly employed in a variety of situations, such as decision-making in the face of affective information or inhibition of inappropriate responses within the

context of an ever-changing social environment (Jurado and Rosselli, 2007). Understanding how social information interacts with cognitive control has implications for a variety of psychiatric disorders characterized by disruption of both cognitive control and social cognition, such as autism. Despite recent interest in understanding the interplay between these two cognitive domains, most research has focused on how social information promotes goal-directed behavior. Little is known about how social information interferes with cognitive control when it is not relevant for the ongoing task or how this may contribute to deficits associated with autism.

The goal of this research was twofold: the first aim was to utilize functional magnetic resonance imaging (fMRI) to examine how neurotypical individuals integrate social and executive neural network processes that are competing for finite attentional resources during a cognitive control paradigm in which the social context is not relevant to performance on the task. The second aim was to utilize the same fMRI paradigm to probe the interaction between the social and executive neural networks in a group of individuals with autism, relative to the neurotypical control group. Elucidating the neural underpinnings of how individuals with autism differentially resolve competition between executive and task-irrelevant social information may provide insight into the increased difficulty that individuals with autism exhibit when performing executive tasks administered within a social context.

The following introduction will provide a framework for understanding this interaction by first discussing the phenomenology and neural underpinnings of the social deficits in autism. Following this will be an outline of executive and selective

attention deficits in autism and a description of how the paradigm utilized in the current research, the oddball task, probes these cognitive constructs. Finally, previous research on the interaction between social and executive processes will be highlighted and this will provide a framework with which to understand the rationale for the current body of research.

1.1. Social Cognition Deficits in Autism

Autism is a complex and heterogeneous neurodevelopmental disorder characterized by impairments in social cognition, language and communication difficulties, and the presence of restricted interests and repetitive behaviors (American Psychiatric Association, 2000). Recent estimates suggest that autism affects 1 out of every 110 individuals, making it more common than pediatric cancer, diabetes, and AIDS combined (Centers for Disease Control, 2009). The social impairments, repetitive behaviors, and restricted interests characteristic of autism are suggested to be associated with more basic deficits in social cognition and executive function.

Of the core symptom domains, the defining deficit in autism is the impairments in social behavior and cognition (Adolphs, 2001; Schultz, 2005). Findings suggest disruption of higher-level social cognition in autism, with the sparing of more basic processes. Evidence that individuals with autism do not have difficulty discriminating faces based on identity or emotional intensity supports this. Specifically it suggests that individuals with autism have intact visuoperceptual abilities with respect to face processing. Individuals with autism do exhibit several

other social cognitive deficits, such as difficulties identifying emotional facial expressions and an inability to use gaze-information to infer mental states (Adolphs et al., 2001; Baron-Cohen et al., 1997; de Jong et al., 2008). Additionally, one of the most replicated findings has been that individuals with autism utilize differential scanning patterns for social stimuli, attending to the mouth to a greater extent than the eyes or attending to non-social objects in a scene (Dalton et al., 2005; Jones et al., 2008; Klin and Jones, 2008; Klin et al., 2002; Klin et al., 2009; Nacewicz et al., 2006; Neumann et al., 2006; Pelphrey et al., 2002).

1.1.1. Neural Circuitry Underlying Social Deficits in Autism

The neural circuitry mediating social cognition, which underlies the processes involved in face perception and recognition, as well as emotion identification, rapidly develops over the first six months of life in neurotypical children (Dawson et al., 2004b). Neuroimaging and lesion studies have implicated a number of predominantly right lateralized regions in the social processing network including the fusiform cortex (FFC) and superior temporal sulcus (STS), which are involved in the identification of the invariant and changeable aspects of faces, respectively. In addition to regions specialized for face detection, the amygdala, ventromedial prefrontal cortex (vmPFC), ventrolateral prefrontal cortex (vlPFC), orbital frontal cortex (OFC), and cingulate have all been implicated in the incorporation of social information with cognitive and motivational processes (Adolphs, 2001). In addition to the broader cortical social neural network, there is evidence for a subcortical processing system, comprised of the amygdala, superior colliculus, and pulvinar nucleus of the thalamus, that is involved in the rapid and automatic processing of

social information (Johnson, 2005). More recent reviews of the data, however, suggest that this subcortical system may not be present in primates, including humans. Instead, it is suggested that processing of social information occurs simultaneously across multiple visual-processing pathways including a network comprised of the amygdala, OFC, anterior insula (AI), and anterior cingulate cortex (ACC), which bias attention towards the salient social stimuli (Pessoa and Adolphs, 2010).

The amygdala is one of the primary structures associated with processing social information and is involved in a number of social cognitive functions, including spontaneously directing attention to the eye regions of faces, as well as coordinating with the striatum and OFC to monitor and update the social significance of stimuli (Itier and Batty, 2009; Klein et al., 2009). Most research on humans with amygdala lesions have been difficult to interpret due to the lack of specificity of the lesions, a problem associated with many lesion studies in both humans and non-human primates. Despite this, Urbach-Wiethe disease is a rare genetic disorder which results in lesions to the amygdala with limited effect on surrounding cortex (Adolphs et al., 1999). Much research has investigated the role of the amygdala in social, affective, and motivational behavior in a small subset of patients with this disease, with particular focus on a single patient, “SM.” A summary of the findings from research with patient SM was recently reviewed and include an impaired ability to identify emotion in static pictures of faces and eyes, abnormal ratings of trustworthiness and the intensity of emotion in fearful faces, and abnormal scanning of faces characterized by increased fixation on mouths (Adolphs, 2010). While this

suggests that the amygdala contributes to social processing, it is likely that the primary function of the amygdala is to more broadly assess perceptual stimuli for their relevance, including their affective and social value, and then integrate that information with cognition and behavior (Adolphs, 2001, 2010).

The similarity between individuals with amygdala damage, such as "SM," monkeys with early postnatal ablation to their amygdala, and individuals with autism suggests a role of the amygdala as a contributing factor in the social deficits in autism (Baron-Cohen et al., 2000). For example, individuals with autism have been reported to have stronger reactions to typically non-threatening situations and decreased reactions in instances where typically-developing individuals would usually exhibit fear (Bachevalier and Loveland, 2006). Additionally, they have difficulties regulating their affective responses to both social and non-social stimuli and they perform similarly to individuals with bilateral amygdala lesions on tests of social trustworthiness and approachability, as well as when identifying the emotional features in facial expressions (Adolphs et al., 2002; Adolphs et al., 2001; Graham et al., 2007; Pelphrey et al., 2002). Furthermore, complete ablation of the amygdala in non-autistic individuals results in a significant reduction in time spent fixating on the eyes and increased time fixating on the mouth during social interactions, which is directly comparable to findings for individuals with autism (Spezio et al., 2007).

Several fMRI studies have provided further evidence that the amygdala may be dysregulated in individuals with autism, though there is controversy as to the direction of this dysregulation. The majority of studies have found hypoactivation in the amygdala in response to emotional faces, though this finding has not always

been replicated (Ashwin et al., 2007; Baron-Cohen et al., 1999; Critchley et al., 2000; Pelphrey et al., 2007). For example, in 2005 Dalton and colleagues reported a strong positive correlation between the time that individuals with autism spend fixating on eyes and the activation elicited in both their amygdala and FFC (Dalton et al., 2005). New research suggests that altered habituation of the amygdala to social stimuli may explain some of the discrepancy in functional imaging findings from individuals with autism. Specifically, while the amygdala and FFC of neurotypical participants habituates over repeated presentations of neutral faces, this is not the case for individuals with autism. Furthermore, this lack of habituation is associated with more severe social impairments in individuals with autism (Kleinhans et al., 2009). Together these findings suggest that the amygdala plays an integral role in establishing and maintaining proper social-cognitive responses to environmental cues and that amygdala dysfunction may contribute to the social deficits seen in autism.

In addition to the amygdala, there are also regions within the FFC that are important for face processing. Dubbed the fusiform and occipital face areas (FFA and OFA, respectively), these regions are activated most robustly by face-specific stimuli, though there is some debate as to whether they are “face-specific” processors (Cohen Kadosh et al., 2010; Gauthier et al., 2000; Kanwisher et al., 1997). Models of face processing posit that the inferior and medial occipital gyri process the various components of face stimuli and then the FFC integrates the components. However, there is evidence that the eyes are not integrated with the rest of the face stimulus in the FFC, but instead have their own dedicated neural

network differentially activated based on task demands. Specifically, it is possible that many of the same regions that are important for face processing are also involved in processing eyes, but that the interconnections among these regions is differentiated based on whether the task requires the global (i.e. whole face) processing of the stimulus or local (e.g. eye specific) processing (Itier and Batty, 2009). Studies utilizing fMRI have identified a neural network engaged specifically by direct gaze. This network includes the occipital FFC, right parietal lobe, bilateral middle temporal gyrus (MTG), right amygdala, right pulvinar nucleus of the thalamus, and bilateral medial dorsal nucleus (MDN) of the thalamus (Farroni et al., 2004). Additionally, there are several other temporal lobe structures that are also involved in face processing, including the right inferior temporal gyrus (ITG) and the STS, both of which contain face and eye selective cells and are important for recognizing social cues (Adolphs, 2001; Itier and Batty, 2009; McRae et al., 2010). The specialization of this neural network to process both general social stimuli and the eye region of faces, including processing the direction of eye gaze, highlights the fact that social information is an especially important stimulus class that receives high priority with respect to attentional and cognitive resources.

Much like the amygdala, the FFC has been a region of great interest in the social cognitive research of autism. Several studies have reported decreased activation in the FFC to a variety of social tasks in individuals with autism (Critchley et al., 2000; Hubl et al., 2003; Pierce et al., 2001; Schultz et al., 2000), however this has not always been replicated (Dalton et al., 2005; Hadjikhani et al., 2004; Hadjikhani et al., 2007). It has been suggested that the hypoactivation may be due

to decreased attention to the face stimuli, as evidenced by scan path analysis, as opposed to being associated with a more basic deficit in FFC function (Dalton et al., 2005). On the other hand, there is also evidence that the reason some studies do not find activation differences in the FFC of individuals with autism is associated with a lack of power to detect differences in less cognitively taxing paradigms. Specifically, social cognitive tasks that require only superficial processing of face stimuli may be associated with less engagement of the FFC in neurotypical controls, which may look similar to the hypoactivation found in the individuals with autism. However, during more difficult social cognitive tasks, such as the emotion-morphing task, activation in the FFC of neurotypical participants is much higher and this permits the detection of hypoactivation in the individuals with autism (Schultz, 2008; Schultz, 2005).

A number of paradigms have also provided evidence for a role of the STS in the pathophysiology of autism. The STS is important for processing the changeable aspects of social stimuli. Specifically, it is important for differentiating biological motion from non-biological motion and is involved in utilizing eye-gaze information to infer the mental states of others (Pelphrey et al., 2003; Pelphrey et al., 2004). Individuals with autism have difficulties with both of these social processes and fMRI experiments suggest that it is in part due to aberrant activity within the STS. Specifically, the STS of neurotypical individuals has been shown to activate in response to stimuli that approximate biological motion, but not to stimuli that approximate mechanical motion while maintaining the same perceptual qualities as biological motion. On the other hand, the STS of individuals with autism tends to

activate similarly to both biological and non-biological motion (Pelphrey and Carter, 2008a). Furthermore, the STS of neurotypical individuals has been shown to be more active in conditions where the eye-gaze information of another person is incongruent with respect to what is expected (e.g. if the other person looks away from a suddenly appearing stimulus). On the other hand, the STS of individuals with autism does not appear to make this distinction (For review: Pelphrey and Carter, 2008b; Pelphrey et al., 2005). In addition to the functional differences of STS activation, recent reports suggest that there are also structural differences in the STS of individuals with autism. Specifically, after controlling for both age and total brain volume, the right STS appears to be larger in individuals with autism as compared to neurotypical controls (Jou et al., 2010).

While there are clear differences in discrete regions within the social network of individuals with autism, there is also evidence for aberrant between region functional and structural connectivity. For example, a recent study identified functional connectivity differences in response to a face identification task between the FFC and other social cognition regions, such as the amygdala, in individuals with autism (Kleinhans et al., 2008). This study demonstrated reduced connectivity within the face-processing network of individuals with autism as compared to neurotypical controls. This suggests that the face-processing deficits in autism are associated with poor functional integration of the social cognition neural network. The authors suggest that this may cause individuals with autism to experience an increase in cognitive demand when processing faces, as compared to non-social stimuli (Kleinhans et al., 2008). In addition to these findings, a recent study by Conturo and

colleagues (2008) reported microstructural alterations in the white matter tracts that connect the FFC with the amygdala and hippocampus, despite intact macrostructure (Conturo et al., 2008). Taken together, this suggests that aberrant functional and structural connections between the FFC and other regions within the social neural network, particularly the amygdala, may underlie many of the face processing deficits seen in individuals with autism.

1.1.2. Hypotheses of the Developmental Basis of Social Deficits in Autism

Several hypotheses have been put forth to account for the development of aberrant social processing in the social cognition brain circuits of individuals with autism. One such model posits that an early developmental aberration in the amygdala, as evidenced by the structural findings highlighted above, underlies a decreased bias to attend to faces in infancy (Schultz, 2005). In typical development, humans are equipped with the ability to quickly analyze visual input for social relevance and preferentially attend to direct gaze from birth (Farroni et al., 2002; Itier and Batty, 2009). A neural circuit characterized by the amygdala and related dopaminergic reward networks subserves this early attention to faces. Thus, early attention to faces is associated with a positive reinforcement of the salience of faces to the neurotypical infant and this leads to the development of the expertise in processing faces that is attributed to activity in the FFA and STS (Schultz, 2005). Thus, in the Schultz (2005) model, the aberrant development of the amygdala in infants with autism results in a decreased salience of faces. This leads to a cascade effect whereby individuals with autism do not achieve the same level of experience with faces as neurotypical controls and this results in aberrant social skill

development (Schultz, 2005). In line with this hypothesis, Dawson and colleagues (2005) posit that the lack of attention to faces is driven by an inherent absence of motivation to attend to faces in individuals with autism. This motivational drive relies on the same connections between the amygdala and dopaminergic reward systems identified in the Schultz model, as well as on the orbitofrontal cortex (Dawson et al., 2005; Schultz, 2005).

In a somewhat contradictory model, Dalton, Davidson and colleagues (2005) propose that it is not a failure of the amygdala to assign salience to faces in infancy, but instead a heightened arousal response to social stimuli that accounts for the face processing deficits in autism. Furthermore, they suggest mediation of this increased arousal by hyperactivation in emotional neural circuitry, including the amygdala. Evidence for this model includes activation in the FFA that is equivalent to that seen in neurotypical controls. Additionally, their works suggests amygdala hyperactivation in individuals with autism when controlling for time spent fixating on the eyes or when the task directs participants to fixate on eyes (Dalton et al., 2005; Hadjikhani et al., 2004; Hadjikhani et al., 2007). More recent research supports this hypothesis, suggesting that when measuring eye fixation during an emotion identification task, individuals with autism tend to shift their gaze away from the eyes whereas neurotypical controls tend to shift their gaze towards the eyes. Together this suggests an increased avoidance of the eyes in individuals with autism (Kliemann et al., 2010). Additionally, increased social anxiety in individuals with autism has been linked to increased amygdala activation on an emotional face matching task and this is suggested to be associated with increased avoidance of faces (Kleinhans et al.,

2010). If eye gaze were an aversive stimulus in individuals with autism, one would expect increased activation in the alerting network comprised of connections between the sensory association cortices (e.g. the FFA) and the amygdala, orbital frontal, and anterior cingulate cortices. Specifically, inhibitory GABAergic innervations from the posterior OFC to the intercalated masses of the amygdala would activate further inhibitory signals to the central nucleus of the amygdala. This results in the disinhibition of the hypothalamus and begins a cascade of responses including increased heart rate, increased respiration, and increased sweating (Barbas, 2007). In support of this, research suggests that there is increased physiologic arousal, as measured with skin conductance responses, in individuals with autism when presented with social stimuli, particularly with direct gaze (Joseph et al., 2008; Kylliainen and Hietanen, 2006).

Regardless of whether there is a lack of motivation to attend to social stimuli or whether social stimuli are aversive to individuals with autism, both hypotheses converge on the same neural networks. Specifically, both assume functional dysregulation of the amygdala, whether it be by hyperactivation in response to arousal by social stimuli or by an inability of the amygdala to signal that social information is salient and should capture attention. Both of these mechanisms translate into a lack of attention to social stimuli in infancy that then result in decreased experience with social information. Thus, both models also explain decreased activation in other face sensitive regions, specifically the FFA and STS. Additionally, both of these hypotheses may help explain why individuals with autism have difficulty with cognitive processes within a social context, which will be

discussed in detail in section 1.4. In particular, increased arousal to social stimuli may result in a commandeering of neural resources away from executive networks making it more difficult for individuals to complete an executive task. In a similar fashion, if there is a lack of specialization of the neural circuitry involved in processing social information and an individual with autism must process both social and executive information simultaneously, it may tax the attention systems and increase the cognitive demand required to complete the task.

1.2. Executive Function, Selective Attention, and Autism

While the social cognitive deficits are a defining feature of autism, individuals with the disorder also exhibit a deficit in executive function, which has been linked to their restricted interests and repetitive behaviors (Lopez et al., 2005; Pennington and Ozonoff, 1996; Rinehart et al., 2002; South et al., 2007). Although there is evidence that individuals with autism exhibit deficits in executive function, it is believed that these deficits are secondary to the disorder, meaning that they are not a cause of autism, but instead may be a consequence of having the disorder (Yerys et al., 2007). Executive function refers to higher-level cognitive processes, including behavioral flexibility, planning, as well as inhibitory and cognitive control (Carter et al., 1999). Effective executive function requires motivation, as well as proficiency in problem solving, working memory, impulse control, inhibition, mental flexibility and planning/strategy generation (Casey et al., 2002; Elliott, 2003; Ozonoff, 1995). Much like the clinical manifestation, the profile of executive functions seen in individuals with autism is highly heterogeneous. Specifically, it is characterized by

deficits on some measures of executive function, such as cognitive flexibility, planning, and prepotent inhibition, and yet there are “islets of ability” in other measures including rote memory and interference inhibition (Bennetto et al., 1996; Eigsti and Shapiro, 2003; Hughes et al., 1994; Ozonoff et al., 1994; Prior and Hoffmann, 1990; Rumsey, 1985; Rumsey and Hamburger, 1988).

Data on individuals suffering lesions to the prefrontal cortex (PFC) suggest that the PFC plays a critical role in executive functions. Specifically, damage to the PFC is associated with impairment on numerous measures of executive function such as planning, decision-making, behavioral inhibition, set-shifting, and cognitive flexibility (Goldstein et al., 2004; Owen et al., 1993; Stuss and Benson, 1984; Stuss et al., 2001). Furthermore, damage to the PFC has been shown to result in the emergence of perseverative and repetitive behaviors, insistence for sameness, and impulsivity, all of which are clinical manifestations of autism spectrum disorders (Damasio and Maurer, 1978; Hill, 2004a; Hill, 2004b; Ozonoff, 1995; Ozonoff et al., 1991; Russo et al., 2007; Schmitz et al., 2006). In particular, impairments in inhibitory control and cognitive flexibility may be associated with the perseverative behaviors and obsessionality that is characteristic of autism (Schmitz et al., 2006). These similarities have led some researchers to develop the “executive dysfunction” theory of autism. This theory posits that a primary deficit in PFC function in individuals with autism accounts for the executive, emotional, and social cognitive deficits associated with the disorder (Ozonoff et al., 1991).

Cognitive control is one aspect of executive function often studied in neuropsychiatric disorders, such as autism. Cognitive control refers to the ability to

suppress competing information and behavioral responses, as well as to inhibit prepotent responses and initiate appropriate ones. Thus, a fundamental role of cognitive control in goal-directed processes is to facilitate appropriate behavioral responses through top-down control of attention towards task-relevant stimulus attributes and away from interfering irrelevant information (Casey et al., 2002; Desimone and Duncan, 1995; Miller and Cohen, 2001). Numerous cognitive operations have been implicated in the successful implementation of cognitive control, including goal maintenance, response inhibition and selection, flexibility, as well as performance and conflict monitoring (Botvinick et al., 2001; Goghari and MacDonald, 2009; Paxton et al., 2008; Ridderinkhof et al., 2004; Rougier et al., 2005). As previously reviewed, many of these cognitive operations, including cognitive flexibility and prepotent inhibition, are areas of difficulty for individuals with autism.

Each of these cognitive operations plays a different role in cognitive control processes and is rooted in separable, but overlapping neural networks. For example, the maintenance of task-relevant representations in working memory (i.e. goal maintenance), which drives perceptual processing and attention allocation towards relevant stimulus attributes, is largely accomplished in dorsolateral prefrontal cortex (dlPFC) and vlPFC (Paxton et al., 2008). In addition to goal-maintenance, the lateral sections of the PFC are also involved in response inhibition, with the right inferior frontal gyrus (IFG) playing an especially important role (Aron et al., 2004; Goghari and MacDonald, 2009). Response inhibition is important for cognitive control as it is not only involved in inhibition of a prepotent motor response,

but also inhibition of distraction by task-irrelevant information (Ridderinkhof et al., 2004). In addition to lateral PFC, the midline ACC is also important for the cognitive operations underlying successful cognitive control processes. Specifically, the ACC regulates top-down control of goal-relevant behavior via dopaminergic projections to the lateral PFC. These feedback projections are important for updating goal-maintenance processes based on information about current performance and conflict resolution (Botvinick et al., 2001; Lorsbach and Reimer, 2008; MacDonald et al., 2000).

1.2.1. Neural Circuitry Underlying Executive Deficits in Autism

Several studies have set out to identify the neural circuitry that is associated with the executive and cognitive control deficits in individuals with autism. For example, the cognitive inflexibility and perseverative behaviors that are especially prevalent in individuals with autism are associated with a difficulty with disengaging from previous task demands after a paradigm shift (Kana et al., 2007). This is related to an uncoupling of the inhibition network, comprised of the cingulate gyri and the insula, from the frontal-parietal processes in individuals with high-functioning autism (Kana et al., 2007). In addition, explorations of the cognitive set-shifting abilities in individuals with autism suggest that the autism group tends to make more errors and has slower reaction times than neurotypical participants. This behavioral deficit is further associated with hypoactivation in the executive circuitry of individuals with autism, specifically in the dlPFC, ACC, intraparietal sulcus (IPS), thalamus, and basal ganglia. Moreover, correlational analyses reveal that the activation in the ACC and left IPS is significantly negatively correlated to restricted

and repetitive behaviors as measured in the Autism Diagnostic Interval-Revised (ADI-R; Shafritz et al., 2008).

While studies of cognitive set-shifting suggest that the dorsal network of individuals with autism is hypoactive, studies investigating other domains of executive function, namely inhibitory control, have shown that individuals with autism hyperactivate task-relevant executive neural networks as compared to neurotypical participants. Specifically, there is hyperactivation in the frontal cortex, insula, anterior cingulate, and the inferior parietal cortex. Importantly, it is not yet known whether increased activity in these brain regions are due to inefficient recruitment of the dorsal neural network or if it reflects compensatory changes associated with their reliance on alternative cognitive strategies to complete the task (Schmitz et al., 2006).

In addition to alterations in focal regions within the dorsal network, recent research using functional connectivity analyses, which are measures of the level of synchronization between separate brain regions within a broader neural network, have demonstrated that there are circuit-level changes in this system. Specifically, multiple studies have shown that there is decreased functional connectivity between frontal brain regions and areas in the parietal and temporal cortex in individuals with autism. For example, Just, et al. (2004) demonstrated that individuals with autism have decreased functional connectivity between regions associated with language processing, specifically broca's and wernicke's areas, and regions associated with integration of information, such as the dlPFC (Just et al., 2004). Similar findings have been reported for the connectivity between frontal and parietal regions on a

task of sentence imagery (Kana et al., 2006), on the Tower of London task, which is a task of executive planning (Just et al., 2007), as well as on a tasks probing inhibitory control and inhibition of prepotent responses (Kana et al., 2007; Solomon et al., 2009). Together, these findings have led to the proposal that autism is characterized by under-connectivity in fronto-parietal neural networks (Geschwind and Levitt, 2007).

1.2.2. Role of Selective Attention in the Executive Deficits Seen in Autism

Cognitive control processes are not engaged in isolation, but often work in concert with other operations underlying executive functions, such as working memory and selective attention. While there is evidence that memory functions are mostly spared in autism, there is evidence for selective attention deficits in individuals with autism. Indeed, abnormalities in attentional focus have been documented in autism since Kanner's seminal description of children with the disorder (Kanner, 1943). Specifically, it is evident that individuals with autism do not suffer from an overt inability to focus attention because they often focus attention on objects to the exclusion of attention to other salient stimuli in the environment. This led researchers to suggest that autism may be associated with disordered attentional processes (Burack, 1994; Pascualvaca et al., 1998). Many studies have highlighted deficits in the ability of individuals with autism to filter task-irrelevant information and focus attention on goal-relevant stimulus features (Burack, 1994; Ciesielski et al., 1990; Ciesielski et al., 1995; but see Pascualvaca et al., 1998). This has been linked to an inability of individuals with autism to properly focus their "attentional lens" in favor of task-relevant information (Burack, 1994).

The biased competition model of attention, put forth by Desimone and Duncan (1995), provides a framework with which to understand these deficits. Specifically, this model posits that from the time a stimulus is detected to the point when a behavioral response is initiated, objects in the visual space compete for neural processing resources. Additionally, the amount of neural resources available for processing stimuli is directly related to the level of cognitive load imparted by the task (Lavie, 1995). Thus, in high cognitive load tasks, the amount of resources available for stimulus processing is low and thus attention allocation is focused on only the most salient and task-relevant stimuli and task-irrelevant stimuli are thus not processed. Conversely, when cognitive load is low, there are a greater number of neural resources available for processing stimuli, increasing the ability of task-irrelevant distracters to be processed in concert with the task-relevant stimuli (Lavie, 1995).

With this in mind, a recent study suggests that individuals with autism may be able to incorporate more information into their attentional focus before reaching the limits of their perceptual capacity. Thus, based on Lavie's (1995) hypothesis of the effects of perceptual load on selective attention processes, this results in the need to recruit cognitive control mechanisms to inhibit interference by distracting information across a broader range of perceptual load than necessary for neurotypical participants (Remington et al., 2009). According to this hypothesis, it is not a deficit in selective attention that results in the decreased ability to inhibit interference by task-irrelevant distractors. Instead, the enhanced capacity of the attentional system in individuals with autism allows incorporation of more information into the current

attentional focus. This results in the greater reliance on cognitive control inhibitory mechanisms that, as previously reviewed, have been found to be deficient in individuals with autism participants (Remington et al., 2009). In support of this, there is evidence that the attentional filtering of task-irrelevant information in individuals with autism occurs at later processing stages than in neurotypical controls (Belmonte and Yurgelun-Todd, 2003). Thus, this suggests individuals with autism recruit selective attention neural systems to a greater extent than neurotypical controls in order to filter of task-irrelevant information that are within the focus of attention. Specifically, the role of the selective attention system is to bias the analysis of stimulus properties in other neural networks towards those that are currently relevant to behavior (Desimone and Duncan, 1995). Selective attention mechanisms can be broken into bottom-up and top-down processes both of which bias the representation of stimuli in the visual cortex. Specifically, the bottom-up sensory-driven mechanisms, such as stimulus salience, bias attention based on stimulus attributes irrespective of the goal-relevance of the stimulus. On the other hand, the top-down control processes are engaged to overcome the competition from bottom-up responses and thus facilitate processing of the goal-relevant aspects of the stimulus (Pessoa et al., 2002a).

Not surprisingly, there are dedicated neural systems that are associated with the bottom-up and top-down allocation of selective attention. The dorsal fronto-parietal system, which includes the IPS, superior parietal lobule, frontal eye fields (FEF), and dlPFC, is involved in top-down attentional control. Furthermore, it is involved in linking sensory representations to goal-directed motor responses and is

activated in attention demanding target detection tasks (Corbetta and Shulman, 2002; Marois et al., 2004; Pessoa et al., 2002a). The IPS, which has been referred to as the "parietal core of the attention network" (Brazdil et al., 2007) is specifically associated with top-down control of stimulus processing within the visual cortex, resolving perceptual interference and ensuring that the most relevant stimulus properties are attended to while suppressing activity to task-irrelevant distracters (Bledowski et al., 2004; Hopfinger et al., 2000; Marois et al., 2004). Additionally, the FEF, which regulates voluntary shifts in attention, as well as the IPS and the caudal portion of the dlPFC (BA 46), all contain direct reciprocal connections from the visual association cortex. This allows them to directly influence top-down control of visual attention (Barbas et al., 2010; Noudoost et al., 2010). Finally, monosynaptic connections between lateral PFC and the PCC provide a direct route for lateral PFC to impart attentional control, allowing it to be involved in both the selective attention to goal-relevant stimuli as well as the suppression of distracters (Barbas, 2000).

The bottom-up selective attention system, referred to as the ventral attention network, is associated with the right temporoparietal junction (TPJ), as well as ventral middle frontal and inferior frontal cortices. This system is involved in detecting and orienting to the presence of novel, salient and behaviorally relevant stimuli (Bledowski et al., 2004; Corbetta and Shulman, 2002; Pessoa et al., 2002a). The ventral attention network is part of a larger neural network comprised of the AI, ACC, amygdala, substantia nigra, and thalamus, all of which are associated with assessing the salience of stimuli. This broader network sends feedback information to the ventral attention stream, thus biasing bottom-up attentional focus in favor of

the most salient stimuli (Bressler and Menon, 2010). The AI is particularly important in this network, being involved both in the detection of salient task-related stimuli, and in the engagement of the attentional control network (i.e. ACC, vlPFC, and dlPFC). The AI has also been demonstrated to have direct white-matter connections with the posterior cingulate cortex (PCC), which facilitates the processing of the task-relevant stimulus (Menon and Uddin, 2010).

Feedback projections between the TPJ in the ventral attention system and the IPS in the dorsal attention system allow the ventral network to act as an alerting system, overriding top-down attentional control in the dorsal system in favor of salient stimuli that are located outside of the focus of attention (Corbetta and Shulman, 2002; Pessoa et al., 2002a). Similarly, selection of a low-salience target in the presence of attention grabbing high-salience distracters requires the inhibition of bottom-up attentional capture in the TPJ and occipital cortex by activity in the top-down control circuitry. The left IPS is associated with this process by actively down-regulating the response of the occipital cortex to the highly-salient distracter (Kastner and Ungerleider, 2000; Mevorach et al., 2010).

1.3. Exploring Executive Function and Selective Attention with the Oddball Task

One paradigm commonly employed to identify the neural underpinnings of cognitive control processes is the oddball task (Huettel and McCarthy, 2004; Yamasaki et al., 2002). The reliability with which the oddball task elicits selective attention and cognitive control processes makes it a powerful tool for investigating

the neural circuitry underlying cognitive deficits in vulnerable clinical populations (Huettel and McCarthy, 2004). The oddball task is a simple target-discrimination task in which infrequent target and distractor stimuli are presented amongst a series of frequent non-target stimuli (McCarthy and Donchin, 1976; Sutton et al., 1965). The oddball task was originally conceived of as a tool to tap into the executive control processes underlying the updating of working memory. Specifically, Donchin's "context-updating" model suggests that the introduction of unexpected novel, but relevant, stimuli within a stream of previously uniform standard stimuli causes an update of the current context incorporating information about the novel stimulus in working memory (Donchin, 1981; Donchin and Coles, 1988, 1998). In other words, the repetitive presentation of the standard stimuli in the oddball task results in the creation of a working memory context governed by an expectation that subsequent stimulus attributes will match that of preceding stimuli. However, the introduction of novel distracter or target stimuli contradicts this expectation bias, thus resulting in an updating of contextual information in working memory to account for the novel stimulus information.

This context-updating is an important component of cognitive control processes because the representation of the current context in working memory permits the selection of and attention to task-relevant stimuli in the presence of interfering information. Thus, selective attention and cognitive control interact in an oddball task because selective attention allows an individual to attend to and enhance processing of task-relevant information while filtering distracting irrelevant sensory input (Bird et al., 2006; Noudoost et al., 2010). Furthermore, selective

attention is controlled by both top-down cognitive control processes and bottom-up sensory information, both of which are engaged when processing novel target and distracter stimuli (Corbetta and Shulman, 2002). In line with this, Cohen and colleagues (1999) propose that the executive processes underlying context-updating can account for the attention, memory, and inhibitory processes that are associated with cognitive control. Specifically, they suggest that global inhibitory processes are not involved in inhibiting competing task-irrelevant information. Instead, the updating of context representations in working memory influences top-down control mechanisms that bias attentional focus in favor of task-relevant stimulus attributes and away from distracting task-irrelevant information (Cohen et al., 1999).

1.3.1. Neural Underpinnings of the Cognitive Constructs Probed by the Oddball Task

Studies employing fMRI with the oddball task have identified a distributed neural network activated by rare task-irrelevant distracter stimuli. This network is comprised of functionally interactive, but anatomically distinct components, namely the dlPFC, vlPFC, medial prefrontal cortex (mPFC), including ACC, parietal cortex, and posterior hippocampus (Bledowski et al., 2004; Clark et al., 2000). In particular, the mPFC, especially the dorsal ACC (dACC; Brodmann Area (BA) 24/32), has been linked to processes associated with signaling the need for increased engagement of cognitive and attentional control circuitry. Furthermore, the dACC engages the inferior parietal cortex (IPL), which is known to be involved in attentional control processes, as well as the dlPFC (BA 9/46), which is associated with top-down control and promotion of task-appropriate behaviors (MacDonald et al., 2000;

McRae et al., 2010). The co-activation of the dlPFC with the IPL to distracters imparts top-down regulation of attentional processing, allowing the disengagement of attentional focus from the features of the distracter stimulus that share perceptual similarities with the target stimulus. This promotes the identification of the stimulus as a non-target and thus facilitates a task-relevant response (Bledowski et al., 2004). Banich and colleagues (2009) postulate that the dlPFC can be subdivided into posterior and a middle divisions. Within this model, the posterior dlPFC modulates activity in the posterior parietal cortex, tuning attentional bias in favor of the task-relevant stimulus features and away from task-irrelevant information. Alternatively, the mid-dlPFC region has been link to the selection of task-relevant perceptual features that will be used by the posterior dlPFC to guide attentional processing biases and promote goal-directed behavior (Banich et al., 2009).

Novel task-relevant stimuli are associated with activations in the same top-down control network as is activated in response to the task-irrelevant stimuli. However, the task-relevance of the stimuli results in additional activation in target detection networks involved in the contextual integration of the incoming stimulus with a mental representation of target properties (Brazdil et al., 2007). More specifically, target processing has been associated with simultaneous neural activity within the PFC and regions associated with stimulus processing, such as the STS and the visual cortex. In this context, the role of the PFC in target detection is to bias processing along task-relevant pathways that favor attention to goal-specific stimulus attributes (Bledowski et al., 2004; Brazdil et al., 2007; Miller and Cohen, 2001). Furthermore, target stimuli also engage the vlPFC, insular cortex, opercular

cortex, and hippocampus, all of which are involved in comparing the stimulus to the target representation in working memory. Target stimuli also engage the posterior parietal cortex, including the IPS, which is involved in the attentional biasing of neural networks in favor of processing stimulus attributes most likely to impart information relevant to target detection (Bledowski et al., 2004; Brazdil et al., 2007). The interaction between the frontal and parietal regions is bidirectional and likely driven by ACC signals to PFC circuitry, which then act to modulate attention. The ACC is in a unique position to impart attentional control based on cognitive goals as it is characterized by direct connections to attention cortex with alternating bands of cells that project to dlPFC and posterior parietal lobe (Posner and Petersen, 1990). While the ACC is involved in the monitoring of the attentional needs of the system, there is also recruitment of the PCC, which may be involved in maintaining the task-related goals in working memory. Additionally, activity in the PCC that is driven by the ACC is associated with the allocation of attentional resources to the processing systems that will best facilitate the fulfillment of the task goals (Brazdil et al., 2007).

1.3.2. The Oddball Task as a Measure of Executive Processes in Autism

The current research project utilized fMRI to investigate the neural underpinnings of a modified oddball task in both healthy adults and individuals with high-functioning autism. Early studies of the neural underpinnings of cognitive control in both neurotypical participants and individuals with autism utilized the oddball task in conjunction with electrophysiological recordings of scalp electrical potentials. Electroencephalographic (EEG) studies employing the oddball task have described an event related potential (ERP), the P300, which is elicited in response to

infrequent task stimuli. Furthermore, the P300 has been linked to the neural processes underlying assessment of the relevance of stimuli to the current task and subsequent goal-directed decision making processes that influence the behavioral response (Brazdil et al., 2007). Most early EEG studies utilizing the oddball task found abnormalities in the attentionally mediated P300 to auditory and visual versions of the task in participants with autism (Courchesne et al., 1984; Courchesne et al., 1985; Courchesne et al., 1989; Gomot et al., 2008; Kemner et al., 1999; Kemner et al., 1994, 1995; Pritchard et al., 1987; Townsend et al., 1999). Additionally, at least one group has reported a larger response to task-irrelevant novel distracters in a component, the N200, that is associated with perceptual categorization of the stimulus and attention focusing and which has been associated with activity in the mid cingulate (Huster et al., 2010; Kemner et al., 2004). Together, this suggests altered novelty processing and attention to targets in individuals with autism. As hypothesized by Sokhadze and colleagues (2009), abnormalities in the P300 to all novel stimuli further support findings of aberrant attention allocation and reduced discrimination of task-relevant versus task-irrelevant stimuli.

Functional imaging studies employing similar oddball paradigms to those used in EEG studies have begun to elucidate the neural underpinnings of the altered ERP response. One such study identified increased activity in individuals with autism as compared to controls in the neural networks underlying successful auditory target detection, namely the right superior frontal gyrus (SFG), middle frontal gyrus (MFG) and IPS (Gomot et al., 2008). More relevant to the current

paradigm, a study investigating the neural correlates of a visual oddball task revealed hypoactivation in the cognitive control neural networks to target trials (Shafritz et al., 2008). Specifically, in response to target events neurotypical controls activated a neural network including the dlPFC, ACC, IPS, and vlPFC/AI, whereas activity was limited to the vlPFC in individuals with autism. The authors suggest that this hypoactivation supports previously described deficits in cognitive flexibility and inhibition of prepotent response associated with the behavioral shift required by the target conditions (Shafritz et al., 2008). Together, previous research on the oddball task suggests altered neural correlates of attentional control, cognitive flexibility, and inhibition of prepotent responses in individuals with autism.

In summary, previous research on the oddball task has provided evidence for altered novelty processing and attention to targets in individuals with autism. Additionally, there is evidence that decreased fronto-parietal connectivity characterizes autism, thus implicating similar networks to those just reviewed as associated with the cognitive processes targeted by the oddball paradigm. Abnormalities in the ability to detect and flexibly adapt to changes in the environment would likely have major behavioral repercussions, especially in the context of the unpredictability of reciprocal social interactions (Gomot et al., 2008). Thus, the utilization of a modified oddball task in the current research project will help elucidate how differences in the neural networks subserving top-down and bottom-up control, as well as selective attention, change detection, and target processing may contribute to cognitive deficits in individuals with autism.

1.4. Interaction between Executive and Social Processes in Autism

Previous research has largely focused on the social or executive deficits associated with autism in isolation; however, they are not isolated constructs outside of the laboratory. Maintaining a balance between cognitive and social processing mechanisms is integral for appropriate social interactions and for adaptive functioning (Jurado and Rosselli, 2007; Ochsner and Phelps, 2007). For example, executive functions allow us to adapt our behavior and inhibit inappropriate responses within the context of an ever changing social environment and, as such, properly functioning executive processes are necessary for the development of socially appropriate behaviors (Bachevalier and Loveland, 2006; Jurado and Rosselli, 2007). Furthermore, the ability to properly regulate behavior within a social interaction requires intact inhibitory processes in order to block inappropriate behaviors (Geurts et al., 2009). Additionally, flexibility, an executive process, is likely required for social proficiency and it has been suggested that social awareness may in turn contribute to executive abilities (Hill, 2004a; Ozonoff, 1995). Thus, it has been argued that executive functions mediate social behaviors in autism and that executive abilities predict long-term social outcome in individuals with autism (Berger et al., 1993; McEvoy et al., 1993; Ozonoff, 1995).

Several studies report connections between executive function and theory of mind abilities in both typical development and in autism, thus supporting an interaction between social and executive processes (Joseph and Tager-Flusberg, 2004; Ozonoff et al., 1991; Pellicano, 2007). Theory of mind (ToM), which is deficient in autism, refers to the ability of an individual to attribute mental states to

oneself and to others and to understand that others have mental states that are different from one's own. It is hypothesized that intact executive functions, particularly set-shifting abilities, are essential for later development of ToM skills. This is based on a double dissociation whereby impairments in ToM have been found in the absence of executive impairments, however there is no evidence for intact ToM in individuals with impaired executive functioning (Pellicano, 2007).

In addition to the connections between executive function and ToM, a recent study (Allen and Barchard, 2009) has shown that individuals with autism exhibit worse performance than neurotypical participants on a "social cognition" factor of intelligence. This factor is comprised of the social content of the Picture Arrangement and the Picture Completion subtests of the Wechsler Child and Adult Intelligence Scales. Both of these subtests have previously been shown to require intact functioning of executive neural circuitry, specifically the PFC, while also tapping into the cognitive processes underlying adaptive social behavior (Allen and Barchard, 2009; Goldstein et al., 2008; McFie and Thompson, 1972). Together, this suggests an intricate link between social cognition and executive function in individuals with autism.

1.4.1. Neural Underpinnings of the Integration of Social and Executive Processes

Integration of social cognitive and executive processes is dependent upon strong reciprocal connections between the amygdala and the OFC/caudal medial PFC, which then relays information to other frontal regions including the ACC, vlPFC, and dorsomedial PFC (dmPFC; Banks et al., 2007; Barbas, 2000). Maintaining the appropriate balance between social and cognitive processes

requires these neural systems to be available for recruitment in selective and flexible ways that best fit the current circumstances (Barbas et al., 2010). The flexibility of these interactions allows for the control of interference by social information when it competes with attainment of a current goal. It also allows for attention to social information at the expense of cognitive processes when that information is important, but outside of the current focus of attention.

The amygdala is involved in determining the social or affective value of stimuli, as well as in cognitive functions like attention and decision-making. Thus, the amygdala plays a pivotal role in integrating social and cognitive processes (Pessoa, 2010). The high level of amygdala connectivity with other brain regions makes it an important link between social affective processing and cognitive control and places it in a prime position to regulate the flow of information between social and cognitive networks (Pessoa, 2008). For example, the basolateral nucleus of the amygdala receives substantial bidirectional input from sensory cortices and has feedback projections to attentional and executive processing systems in the parietal, cingulate, insular, and prefrontal cortices (Pessoa, 2010). This places the basolateral amygdala in a unique position to function as a conduit between the social and cognitive neural networks. Thus, the amygdala provides information on both the social salience of incoming sensory information, and the goal-directed relevance of the stimuli. Together this influences the balance between the bottom-up attentional influence of salient social information and the top-down attentional influence of task-related expectations. Pessoa and colleagues hypothesize that the amygdala is a “hub” region that takes stimuli already evaluated for its cognitive,

social and motivational value, and integrates it with other sensory information. It then projects that information to the prefrontal cortex, specifically the lateral PFC, ACC, and OFC (Pessoa, 2008, 2010).

Along with the amygdala, the OFC receives polymodal innervation from sensory cortices making it a prime recipient of highly processed sensory information (Barbas, 2000). Strong reciprocal connections between sensory cortices and the amygdala/OFC allow these regions to integrate highly processed sensory information. Subsequently, they send feedback information about the behavioral and social significance of the stimulus to the sensory cortex, thus biasing later-stages of perceptual processing (Pessoa, 2008; Pessoa et al., 2002a). In addition to the direct innervation of sensory cortices to the OFC, there is also a pathway from the amygdala, through the thalamus, to the OFC. This pathway allows the amygdala and OFC to flexibly update the significance of stimuli as related to current goals, which in turn can drive attentional focus away from distracters and towards salient or goal-directed stimuli (Barbas et al., 2010). As a result of these connections, the OFC along with the closely related vlPFC and vmPFC, incorporates social information into decision-making when appropriate and recruits cognitive control mechanisms to inhibit information not relevant to current goals (Beer et al., 2006b).

As another direct target of the amygdala, the ACC also plays an important role in integrating social and cognitive information, especially in the top-down regulation of affective responses interfering with ongoing goal-directed behavior (Blair et al., 2007). This region is important in regulating social and cognitive integration due to its role in multiple cognitive processes including attention,

motivation, and behavioral regulation, as well as its influence on affective control (Barbas et al., 2010; Bush et al., 2000; Clark et al., 2000). The cognitive and social functions of the ACC are associated with discrete, but interconnected sections of the ACC based on the regions that each of these sections project to. Specifically, the dACC has been designated the "cognitive division" of the cingulate because it, along with adjacent dmPFC regions, makes connections with networks involved in cognitive processes, namely the lateral PFC and motor cortices. On the other hand, the ventral ACC (vACC) and rostral ACC (rACC) are considered the "affective divisions" of the cingulate due to their connections with ventral social regions, particularly the amygdala (Etkin et al., 2006). Further supporting the division of the ACC into cognitive and affective regions, studies have shown that these two subdivisions are activated reciprocally to one another, with vACC activation and dACC deactivation in response to social stimuli and dACC activation with vACC deactivation during cognitive tasks (Bush et al., 2000; Etkin et al., 2006). Additionally, several studies have shown that the rACC is especially activated in situations where there are task-irrelevant social distracters that need to ignored and that successful inhibition of this distraction is correlated with a concomitant decrease in amygdala activity (Blair et al., 2007; Etkin et al., 2006; Vuilleumier et al., 2001).

Despite evidence suggesting functional and structural divisions of the ACC, other research suggests that the same ACC regions integrate both cognitive and affective information. Several studies have identified activity in the dACC in response to task-relevant social stimuli (Dichter et al., 2009b; Vuilleumier et al., 2001). Additionally, single-cell recordings in humans has shown that dACC neurons

are modulated similarly by attention-demanding tasks, even when those tasks contain affective information, suggesting that the dACC is involved in response to salient stimuli regardless of the affective content of that stimuli (Davis et al., 2005). Together, this suggests that the dACC is involved in processing both social and cognitive stimuli. A recent review of the literature further supports this assertion, and suggests that dACC and vACC are involved in both cognitive and emotional functions, but that the dichotomy is based on their roles in conflict evaluation and conflict regulation, respectively (Etkin et al., 2010). Despite the ongoing debate over whether discrete sections of the ACC integrate social and cognitive information, the importance of the ACC in modulating social and cognitive responses is widely accepted.

1.4.2. Role of Selective Attention in Mediating the Integration of Social and Executive Processes

Under most circumstances, social information tends to capture attentional resources regardless of the task-relevance of the stimulus. Indeed, social cues comprise highly salient stimulus classes that capture attention at an early processing stage, recruit dedicated neural circuits, and are generally selectively attended to at the expense of attention to other non-social and non-affective stimuli (Norris et al., 2004). Thus, social information is a strong driver of bottom-up attention. This effect is largely mediated by the amygdala's response, which results in prioritization and modulation of responses to the social stimulus in both early visual cortex as well as higher-order visual processing regions such as the anterior ITG and FFC (Pessoa, 2010; Vuilleumier et al., 2001).

The reallocation of attentional resources towards social stimuli transiently biases cognitive control processes even when the stimuli are not relevant to the goals of the current task. This has been shown to interrupt goal-directed processes in multiple cognitive domains, including working memory and target detection (Dolcos et al., 2008; Dolcos and McCarthy, 2006; Gray et al., 2002; Vuilleumier et al., 2001). Specifically, when both target and distracter stimuli contain affect-laden content, there is recruitment of ventral social neural networks, such as the amygdala and the FFC, regardless of the focus of attention (i.e. whether the affective stimulus is a target or a task-irrelevant distracter). Conversely, dorsal executive control circuitry, including the IPS, supramarginal gyrus (SMG) and PCC, are activated in response to target stimuli irrespective of whether the stimulus contain affective information or not. Interestingly, there is overlap between affective and cognitive processes in a single region, the ACC, suggesting that this region is important for linking these two networks. This permits the ACC to functionally integrate attentional and affective processes and allows affective context to influence goal-directed control of behavior (Fichtenholtz et al., 2004; Gray et al., 2002; Yamasaki et al., 2002).

While it is clear that social cues capture attention relatively automatically (i.e. processing of social information is prioritized over processing of other stimuli), there is some debate as to whether top-down cognitive processes can attenuate the attentional capture by social stimuli (Banich et al., 2009; Mitchell et al., 2007). There are two views regarding the automaticity of social stimulus processing: As previously reviewed the first views posits that social stimuli are automatically processed outside

of the influence of top-down cognitive control within a subcortical pathway comprised of the superior colliculus, the pulvinar nucleus of the thalamus, and the amygdala. This viewpoint is supported by evidence that affective faces activate the amygdala when they are not the focus of attention, as well as when they are presented outside of conscious awareness (Pasley et al., 2004; Vuilleumier et al., 2001). Despite this, there is evidence that increased processing load diminishes the availability of attentional resources (i.e. Lavie's Hypothesis). This results in the top-down, goal-directed modulation by the posterior parietal cortex and dlPFC of regions fundamentally involved in social processing, such as the IFG, vmPFC, and amygdala. This may occur either through modulation of the amygdala response to the social stimuli via direct connections from the vmPFC or through increased processing of task-relevant stimulus features in the temporal cortex as modulated by lateral prefrontal and parietal cortices (Mitchell et al., 2007; Pessoa et al., 2002a; Pessoa et al., 2002b).

Indeed, while social and cognitive information integrate under many circumstances, there are situations in which the social information is not relevant to the task and interferes with task performance. The ability to inhibit interference by social information irrelevant to current goals requires top-down control of ventral social systems by frontoparietal neural networks. Strong anatomical connections between the frontal and parietal cortices allow for the integration of selective attentional signals that engage inhibitory connections between the frontal cortices, particularly the OFC and dmPFC, as well as social processing regions, such as the amygdala and IFG. This results in blunted amygdala activation and the inhibition of

interference by task-irrelevant social information (Banks et al., 2007; Blair et al., 2007; Ochsner and Gross, 2005). Prioritization of goal-directed processing is associated with a reduction in the activity in the IFG/vlPFC (BA 46) and bilateral amygdala in response to affective stimuli (Blair et al., 2007). While this would suggest that the interaction between the amygdala and the IFG/vlPFC is important for the detection and processing of social information, there is also evidence that the vlPFC, particularly in the left hemisphere, also plays an active role in down-regulating the effect of social distraction on cognitive processes. This may occur through either the direct modulation of amygdala activity through influence on other prefrontal regions that are involved in cognitive reappraisal processes or through interactions with the thalamus which can bias the sensory signals that are filtered through attentional control mechanisms (Barbas et al., 2010; Dolcos et al., 2006; Wager et al., 2008).

1.4.3. Dual Network Model of the Integration of Social and Executive Neural Processes

Current information on the interaction between social and cognitive control processes has led to the conceptualization of a dual network model characterized by a dorsal executive control system (DECS) involved in processing executive information and a ventral social-affective processing system (VSAPS) that is critical for processing both social and affective information (Dolcos et al., 2008; Dolcos and McCarthy, 2006; Fichtenholtz et al., 2004; Yamasaki et al., 2002). While these two networks are specialized for processing distinct cognitive information, they integrate attentional, executive, and social information through critical nodes that lie at the

interface of these systems, namely the ACC, dlPFC, vlPFC, vmPFC, and OFC (Beer et al., 2006a; Fichtenholtz et al., 2004; Pessoa, 2008; Yamasaki et al., 2002). Within this framework, the dlPFC, OFC, and lateral parietal cortex are involved in the inhibition of task-irrelevant information, with the dlPFC and OFC imparting this control through their connections with the thalamus, allowing them to bias attentional processes towards task-relevant stimulus features (Barbas et al., 2010; Dolcos and McCarthy, 2006; Miller and Cohen, 2001).

The interaction between these two systems is critically involved in not only integrating information that is both executive and social in nature, but also in maintaining a balance when task-irrelevant social information competes with the goal-directed executive processes for attentional resources (Dolcos et al., 2008). Specifically, when a goal-directed behavior competes with a task-irrelevant social distracter, there is evidence of deactivation in the DECS, including dlPFC, lateral parietal cortex, and PCC. This deactivation is paired with increased activity in the VSAPS, particularly the amygdala, vmPFC, and vlPFC. This suggests that the activity in the VSAPS may temporarily interfere with the ability of the DECS to complete goal-relevant processes thus interrupting cognitive performance (Dolcos and McCarthy, 2006). Therefore, there is likely a biasing of the balance between cognitive and social processes, whereby early processing of distracting social information transiently increases activity in the amygdala and vmPFC. Subsequently, this actively inhibits the dlPFC. Then, in order to overcome the interruption of goal-directed processes, the left vlPFC and right dlPFC are activated to inhibit distraction by the affective information. Simultaneously, parietal attentional

regions act to direct the attentional resources away from the distracting stimulus and towards the task-relevant information (Dolcos et al., 2008; Dolcos et al., 2006; Dolcos and McCarthy, 2006; McRae et al., 2010).

1.5. Rationale and Hypotheses

Many previous studies have established anatomical and functional differences in neural circuitry associated with social cognition and cognitive control in individuals with autism. However, as just reviewed, these studies have almost exclusively examined these networks in isolation. In a novel approach, Dichter and Belger (2007) altered a non-social cognitive control task so that the standard stimuli (arrows) were replaced with social stimuli (eyes) in half of the trials. This study established that the use of social as opposed to neutral arrow stimuli adversely influences cognitive control neural networks in individuals with autism. Specifically, in response to the trials containing eyes, individuals with autism exhibited hypoactivity in cognitive control regions. Specifically, hypoactivity was reported for the IFG, MFG, ACC, and IPS, all of which are important for top-down attentional control and the integration of social and executive information (Dichter and Belger, 2007). In a more recent study, Dichter and colleagues (2009a) employed a variation of the oddball task in which targets were shapes in some trials and neutral faces in others. Behaviorally, individuals with autism were less accurate, but faster to all target conditions. This was associated with increased activation in the comparison of face targets to shape targets in the individuals with autism in a network comprised of the right MFG, right IFG, and the dmPFC/dACC. The authors suggest that this

increased activation represent compensatory mechanisms that permit the participants with autism to perform the task or may be associated with 'cortical inefficiency' (Dichter et al., 2009a). Together, these studies provide clues to the functional alterations associated with the difficulty that individuals with autism exhibit when utilizing social cues, specifically eye gaze, to complete a cognitive task. However, neither of these studies addresses the question of whether the presence of a social context that is irrelevant to the cognitive control task will also result in altered neural network activity in individuals with autism. This distinction is subtle, yet important in light of evidence that individuals with autism have greater deficits on tasks historically considered to tap into PFC functions, such as the Wisconsin Card Sorting Task (WCST), when administered within a social context (Ozonoff, 1995). This has very specific real-world implications for individuals with autism, particularly in a school setting where much of the instruction and feedback they receive will be social in nature. If this social context is distracting or inhibits their ability to complete cognitive tasks, then this may result in these individuals being less likely to succeed.

In light of this, the current body of research aimed to investigate the neural underpinnings of cognitive control processes when those processes are competing with task-irrelevant social information for neural resources in both control participants and in individuals with high-functioning autism. A modified version of the oddball task was developed in order to test this relationship in both groups. This modified oddball contained three novel conditions: a distracter condition comprised of images of neutral eyes with direct gaze (Eyes Alone), a condition in which the target was overlaid on a neutral background (Target Alone), and a target condition

that overlaid the target stimulus on the novel eye stimuli that was a task-irrelevant background image (Target Eyes). Participants were instructed to ignore the task-irrelevant background information and make differential motor responses to target as compared to non-target condition. Importantly, each of the novel stimulus categories was presented an equal number of times, such that the presence of the eyes was not predictive of whether the current trial would be a target.

The oddball task employed in the current project was different from oddball tasks utilized in the previously reviewed studies by Shafritz (2008) and Dichter (2009a) in a few important ways. Specifically, as already highlighted, the standard oddball task probes prepotent response inhibition, initiation of a novel motor response, context-updating of working memory, and selective attention to stimuli. The task employed by Shafritz and colleagues (2008) probed all the same cognitive constructs as the standard oddball, but also had a cognitive switch component. Specifically, in this task the target stimulus was changed periodically, which required the ability to switch the representation of the target stimulus in working memory and to be able to inhibit a previously learned stimulus-response relationship mapping (Shafritz et al., 2008). The paradigm utilized in the study by Dichter and colleagues (2009a) built upon the Shafritz study by adding a social component, whereby the targets or distracters could also be faces. This therefore probed all of the same cognitive constructs as the previous study, with the added effect of the social component that was task-irrelevant in some trials and task-relevant in others (Dichter et al., 2009a). The oddball paradigm utilized in the current study therefore differed from these previous tasks in two ways: 1) it did not include a cognitive

switch condition (i.e. the target stimulus remained the same throughout the task) and 2) the social stimuli were never targets, but were task-irrelevant distracters in the background of a subset of both target and non-target trials.

The design of the oddball task in the current study thus permitted the investigation of a number of the constructs underlying cognitive control and selective attention, as well as the integration of social and cognitive information in neurotypical controls and in individuals with autism. Specifically, the Eyes Alone condition permitted the investigation of the effect of the task-irrelevant eyes on stimulus processing independently of the need to make a novel motor response, and thus was a measure of the level of interference imparted by the eyes on general stimulus processing. The Target Alone condition permitted the identification of the behavioral trade-off associated with inhibition of a prepotent response and initiation of a novel motor response independently of the effect of the task-irrelevant eyes. Finally, the Target Eyes condition provided a measure of the additive effect of pairing the need to inhibit a prepotent response and the need to initiate a novel motor response with the added cognitive requirement of inhibiting interference by the task-irrelevant eyes. Thus, when compared to the Eyes Alone Condition, this permitted the investigation of the effect of the need to inhibit the prepotent motor response in the presence of a task-irrelevant eye distracter. Furthermore, as compared to the Target Alone condition, this permitted the dissociation of the effect imparted by the interference by the eyes, which was specific to the Target Eyes condition, and the effect of the need to inhibit the prepotent response, which was the shared between the Target Alone and the Target Eyes conditions. Finally, when the Target Eyes condition was

compared to the combination of the Target Alone and the Eyes Alone conditions, it permitted the identification of the unique effect of pairing the task-irrelevant eyes with the target, thus providing information on the effect of the need to both inhibit the task-irrelevant eyes and the prepotent motor response.

This task was administered while individuals underwent a functional neuroimaging scan, allowing for the elucidation of neural correlates underlying the interaction between the social and cognitive processes. The first set of analyses considered within and between condition regional effects in each group separately. This was followed by analyses to identify regional differences between the groups in response to task conditions. Finally, functional connectivity analyses were completed in both groups in an effort to elucidate network level differences in the response to the interaction between social and executive neural circuitry.

Based on previous research, it was hypothesized that the behavioral response to the Eyes Alone condition in the neurotypical controls would be similar to that of the standard stimuli based on the lack of a shift in motor response. Furthermore, it was expected that this condition would activate social networks, including the amygdala and FFC, as well as the neural circuitry involved in context updating and processing of task-irrelevant distracter stimuli, specifically the dlPFC, vlPFC, vmPFC, ACC, parietal cortex, and posterior hippocampus. It was further hypothesized that behavioral responses to the Target Alone condition would be slower and less accurate than responses to both the Eyes Alone and the Standard stimuli. This was based on the greater requirement for cognitive control involved both in comparing the stimulus to the representation of the target, as well as a need

to inhibit the prepotent behavioral response and initiate a novel motor action. This condition was anticipated to activate the attention and target detection networks, which include the dlPFC, vlPFC, insular cortex, opercular cortex, and hippocampus, as well as the ACC, PCC, and posterior parietal cortex, including the IPS. Additional activations were expected in the anterior insula, amygdala, and thalamus, all of which are associated with assigning salience to stimuli. Finally, based on the findings from Dichter and colleagues, better accuracy was expected to the Target Eyes as compared to the Target Alone condition in neurotypical controls (Dichter and Belger, 2007; Dichter et al., 2009b). Despite better accuracy, slower reaction times were predicted in this condition because greater cognitive control would be required as the social stimuli would be capturing attention and directing it away from the target stimulus. It was anticipated that this would be associated with preferential activation in the dACC, replicating the Dichter (2009b) results. Additionally, it was projected that there would differential activation of the ventral social and dorsal executive control systems, whereby increased activity in one would be associated with decreased activity in the other. The direction of this effect was not hypothesized, as it was unknown how a task-irrelevant neutral social stimulus would interact with cognitive processing systems. However, it was expected that increased reliance on top-down attentional control and inhibition of interference by task-irrelevant social information would be associated with increased activity in the dlPFC, vmPFC, OFC, thalamus, and lateral parietal cortices and decreased activity in the IFC/vlPFC and amygdala. On the other hand, it has been shown that the reallocation of attentional resources towards social information can transiently bias

cognitive control processes, even when the stimuli are not relevant to the goals of the current task. At the neural level this would be evidenced by decreased activation in the dorsal executive control system, including dlPFC, lateral parietal cortex, and PCC and increased activation in the ventral social processing system, particularly the amygdala, vmPFC, and vlPFC. Finally, it was expected that there would be significant reciprocal correlations between the dorsal executive and ventral social affective processing systems in the functional connectivity analyses in the neurotypical control group and that these connections would be altered in the individuals with high-functioning autism.

It was hypothesized that accuracy to the Eyes Alone condition in the individuals with autism would be similar to that of the neurotypical controls since there is no shift in motor response. Based on previous research and the theory that social stimuli may increase arousal in individuals with autism (Dalton et al., 2005), it was expected that reaction time to this condition would be slower than that of neurotypical controls. With respect to the functional data, it was anticipated that individuals with autism would activate FFC to an equal extent to that seen in neurotypical controls because the short stimulus duration and the placement of the target between the eyes facilitates foveation of the social stimulus. Additionally, if the Dalton (2005) theory of eye processing is correct, it was predicted that there would be increased amygdala activation to the Eyes Alone in individuals with autism. In the Target Alone condition, it was expected that deficits in cognitive flexibility and inhibition of prepotent response would result in decreased accuracy and slower reaction time in the group with autism. Additionally, based on previous research with

the oddball task in autism, it was anticipated that this would be associated with hypoactivation in cognitive control neural networks, specifically in the dlPFC, ACC, and IPS. Furthermore, it was hypothesized that individuals with autism would not show the same behavioral benefit as the neurotypical controls to having a social stimulus paired with the cognitive task. Instead, it was expected that individuals with autism would have equal or slightly worse accuracy to the Target Eyes condition as compared to the Target Alone condition and that this would be associated with slower reaction times to Target Eyes. These behavioral results were projected to be associated with increased activity in the ventral social affective system, which would interfere with cognitive processing and thus result in decreased activity in dorsal attentional and executive control networks. Finally, there is a hypothesis that autism is characterized by local over-connectivity and long-range under-connectivity, with fronto-parietal, fronto-temporal, and fronto-limbic connections being especially aberrant (Geschwind and Levitt, 2007). Thus, it was hypothesized that functional connectivity analyses of activation to the Target Eyes condition in individuals with autism would reveal decreased long-range connections between fronto-parietal, fronto-temporal, and fronto-limbic systems. Additionally, it was believed that disconnection in these networks would be associated with the inability of individuals with autism to exert top-down attentional and cognitive control over the task-irrelevant social context.

CHAPTER 2. METHODS

2.1. Participants

Fourteen male and one female neurotypical participants were recruited through the Duke-UNC Brain Imaging and Analysis Center (BIAC) subject registry and through local advertisements. One subject's data were excluded because there were not enough correct trial events to be analyzed. The single female subject was omitted from all analyses completed on the neurotypical group that were not compared to the autism group (i.e. results sections 3.1-3.3). The purpose of this omission was simplification of data interpretation, which was free from gender confounds. Fourteen male and one female diagnosed with high-functioning autism or Asperger's disorders were recruited through the Subject Registry Core of the Carolina Institute for Developmental Disabilities at the University of North Carolina, Chapel Hill. Participants with autism were matched to the neurotypical group on handedness (thirteen participants were right-handed and two were left-handed), age, and IQ. Diagnoses were based on medical history report and were confirmed through the Autism Diagnostic Interview-Revised (ADI-R) parent interview (Lord et al., 1994) and individual behavioral assessment utilizing the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000; Lord et al., 1989). There were no informants available for two individuals and therefore ADI-R scores were not available for these participants.

All participants were screened and individuals in the neurotypical group were excluded from the study if they reported a history of neurological injury or disease and if they had a history or evidence of mental retardation, neurological impairments, or substance dependence. In addition, neurotypical subjects were screened to ensure they did not meet criteria for DSM-IV psychiatric or substance abuse disorder. Finally, neurotypical individuals with a family history of psychiatric illness or a first-degree relative with a history of psychiatric illness were excluded from the study. As an added precaution, current psychological status was gauged using the Symptom Checklist-90-Revised, which is a 90-question survey that evaluates for a range of psychological symptoms. Individuals with autism were excluded from the study if they were intellectually impaired (estimated IQ less than 70), if they had a known neurological disorder (e.g., Fragile X syndrome, tuberous sclerosis, neurofibromatosis, phenylketouria, or epilepsy), if they had a history of gross brain injury, as well as if they presented with MRI contraindications or had a history of previous psychotic disorder, treated or untreated. Data from one subject in the neurotypical group was excluded because there were not a sufficient number of analyzable trials. This was due both to low accuracy to targets (31% accuracy to the target trials) and equipment failure that required the exclusion of the final functional run. Data from a single subject with autism was also excluded due to extremely low task accuracy (18% accuracy to the target trials). Subjects were consented to a protocol approved by both the UNC-Chapel Hill and the Duke University Medical Center Human Investigations Committees and were paid $60 for participation in the study.

Participant demographics are summarized in Table 2.1. All participants had normal or corrected-to-normal vision. Thirteen participants in each group were right-handed and two from each group were left-handed. Neurotypical participant's ages ranged from 19-37 with an average (s.d.) age of 27.60 (6.56) years. Additionally, all participants were administered the Weshler Abbreviated Scales of Intelligence (WASI; Weschler, 1999) and had full scale IQs $\geq$ 105, with an average (s.d.) whole scale IQ of 116.60 (8.24), verbal IQ of 112.53 (7.38), and performance IQ of 117.40 (10.26). Autism participant's ages ranged from 18-52 with an average (s.d.) age of 27.33 (10.38) years. Additionally, participants were administered the WASI and were shown to have full scale IQs $\geq$ 79, with an average (s.d.) whole scale IQ of 109.36 (13.68), verbal IQ of 106.00 (17.91) and performance IQ of 110.50 (13.44). WASI scores were unavailable for one individual with autism. Participants with autism were matched to the neurotypical participants on age, as well as verbal, performance, and full-scale IQ as measured with the WASI (Weschler, 1999). Appropriate group matching was confirmed via one-way ANOVA. There were no significant effects of age ($F(1, 28) = 0.007$, $p = 0.934$) or group differences on verbal ($F(1, 28) = 1.69$, $p = 0.204$), performance ($F(1, 28) = 2.44$, $p = 0.130$), or full IQ ($F(1, 28) = 2.33$, $p = 0.139$).

2.2. Social Target Detection Neuroimaging Task

The Social Target Detection Task (Figure 2.1) consisted of eight functional neuroimaging "runs," each of which consisted of a series of 124 images presented on a computer screen. There were four categories of stimulus images: standards

(Stan; 88%), Target Alone (Target; 4%), Eyes Alone (Eyes; 4%), and target plus eyes (Target Eyes; 4%). The standard images consisted of scrambled versions of the original full-face stimuli that were used to create the eye images. All trials contained a central fixation shaped as a plus sign, however in 8% of the trials the fixation was rotated by 90 degrees such that it became an X and these were designated target events. Subjects were instructed to fixate at the center of the computer screen and were asked to press a button located under their index finger when they saw a plus sign (+, non-target) and to press a button located under their middle finger when they saw an X (target). Importantly, the Eyes Alone and Target-Eye stimuli were presented an equal number of times so that the presence of eyes was not predictive of whether the stimulus was a target or a non-target. Stimuli from each condition were presented in random order and were spaced 10-14s apart to allow the HDR to reach a peak and return to baseline. All stimuli were presented at jittered interstimulus intervals of 1600-2000ms and each stimulus was presented for 200ms.

.

2.3. Imaging Parameters

Participants were scanned at the Duke-UNC BIAC on a General Electric Signa 3T MRI scanner equipped with high-power 40-mT/m gradients and an eight-channel head coil. Sixty-four high-resolution anatomical images were acquired for later coregistration with functional data using an IR-prepped 3D SPGR sequence (voxel size 2x2x2mm, TR 7.4ms, TI 450ms, TE 2.98ms, Flip angle 12^0, FOV

25.6cm). Whole brain blood oxygen level dependent (BOLD) contrast sensitive functional images were acquired using a spiral-in SENSE pulse sequence (voxel size 4x4x4mm, 32 axial slices, TR 1500ms, TE 27ms, FOV 25.6cm, matrix size 64, Flip angle 60^0). The spiral-in SENSE pulse sequence was selected to optimize signal detection in ventral-limbic and orbito-frontal regions of the brain, most susceptible to field distortion artifacts, and of critical importance for the hypotheses to be tested in this project. The first four volumes (6 s) of each functional run were discarded to allow the magnet to reach a steady state.

2.4. Imaging Analysis

All neuroimaging data were subjected to a processing protocol that included preprocessing to correct for artifacts and reduce noise, as well as coregistration to a standard brain to permit cross-subject comparisons. Following this, data were processed at the subject and group levels for both regional and functional connectivity analyses. The Partial Least Squares (PLS) technique was selected for the functional connectivity analysis. PLS was chosen because it is a data driven, as opposed to hypothesis driven, analysis method. While hypothesis driven methods are focused on utilizing prior knowledge to map connectivity patterns between specific brain regions, data driven analyses study connectivity at the whole brain level and thus are preferable for exploratory analyses (Rogers et al., 2007). Other data driven connectivity approaches include granger causality, psychophysiological interaction (PPI), and principal components (PCA) analyses. PLS was preferable to these other methods due to its relative ease of interpretation, especially as

compared to PCA, as well as its ease of implementation (Rogers et al., 2007). Additionally, while there is some evidence that PPI is less reliable with event-related fMRI (i.e. task designs in which the fMRI images are time-locked to a single stimulus), PLS has been validated for use in event-related fMRI paradigms making it more preferable for the current event-related task (Rogers et al., 2007; Rowe, 2010).

2.4.1. Preprocessing

Images were preprocessed prior to analysis. Head motion was analyzed by center of mass measurements in three orthogonal planes. Imaging epochs with mean intensities greater than two standard deviations of the average intensity in a run were excluded from analyses. Non-brain tissue was deleted from the whole head image using FSL's (Functional Magnetic Resonance Imaging of the Brain [FMRIB] Software Library, version 4.0.3) Brain Extraction Tool (BET; Smith, 2002) and motion correction was completed using FSL's MCFLIRT tool (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The images were then corrected for slice timing and spatially smoothed using a gaussian kernel of full-width half-maximum (FWHM) of 5mm to reduce noise. Additionally, grand mean scaling was completed for intensity normalization and the images were high-pass filtered to remove low frequency artifacts (such as slow signal drift). Each participant's functional images were then coregistered to their high-resolution structural images in native space prior to being normalized into the Montreal Neurological Institute (MNI) standard stereotaxic space using FSL's FLIRT (FMRIB Linear Image Registration Tool; Jenkinson et al., 2002; Jenkinson and Smith, 2001).

2.4.2. Region-Based Neuroimaging Analysis

Region-based neuroimaging analyses were performed using FEAT (FMRI Expert Analysis Tool) version 4.1.5, which is part of FSL (www.fmrib.ox.ac.uk/fsl; Smith et al., 2004; Woolrich et al., 2001). This analysis identifies brain regions that activated in response to each of the task conditions compared to baseline. First- (generation of individual subject fixed effects activation maps), second- (fixed effects analysis averaging across runs), and third-level (mixed-effects analyses to examine group average activations and task contrasts) analyses were completed on correct trials only, using the FEAT tool on FSL version 4.1.5 (Smith et al., 2004; Woolrich et al., 2001). The onset timing for each event was used to model a signal response that contains a regressor for each of the response types and was convolved with a double-gamma hemodynamic response (HDR) curve. General linear model (GLM) fitting was used to generate whole brain images of parameter estimates for each condition (Target, Eyes, Target Eyes).

Activation maps of the main effects were created by calculating an average map based on second level analyses using a mixed effects higher level analysis (FMRIB Local Analysis of Mixed Effects [FLAME 1]) and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.6$ and a Gaussian Random Field (GRF)-theory cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels (Beckmann et al., 2003). In addition to the main effects, additional analyses were completed on the contrast between conditions, namely between the Target Eyes condition and the Target condition, between the Target Eyes and the Eyes condition, and between the Target Eyes condition and the combination of the Target and Eyes

conditions (designated the “Pure Social Target” condition, weighted as 2, -1, -1, respectively, in the GLM). The Pure Social Target condition aimed at identifying brain regions that were differentially activated when the target was paired with the eyes as compared to when either the target or the eyes were presented alone. In an effort to allow greater sensitivity to detect differences between conditions, all condition contrasts were corrected for multiple comparisons using a more lenient Z-statistic threshold of $Z > 1.96$ to identify contiguous voxels, while maintaining a GRF-theory cluster-corrected threshold of $p < 0.05$. A separate uncorrected analysis with a Z-statistic threshold of $Z > 2.3$ (approximately equivalent to an uncorrected $p < 0.02$) was also ran on the Pure Social Target condition to explore regions that may not have survived the original contrast analysis.

Between-group contrasts were analyzed in the same manner as within group contrasts. Group contrast of main effects were analyzed at a Z-threshold of $Z > 1.96$ with a GRF-theory cluster correction of $p = 0.05$. Group contrasts of the condition contrast analyses (e.g. the contrast identifying regions where neurotypical participants show greater activation than participants with high-functioning autism in the Target Eyes > Target condition contrast) were analyzed with an uncorrected Z-statistic threshold of $Z > 2.3$, with the exception of the Pure Social Target condition, which was analyzed at an uncorrected Z-statistic threshold of $Z > 1.961$ (approximately equivalent to an uncorrected $p < 0.05$). Clusters in all uncorrected analyses had to be comprised of at least ten contiguous voxels in order to be considered significant.

Hypothesis driven region of interest (ROI) analyses were completed using the FSL featquery utility within FEAT (FMRIB, Oxford) on data extracted from the second (subject-wise) level analyses described above. Structurally defined ROI masks were identified a priori and included the insula, PCC, occipital FFC, IFC, MFG, and vmPFC as defined in the Harvard-Oxford Cortical and Subcortical Structural Atlases included with the FSL tool package, as well as the IPS, which was defined by the Juelich Histological Atlas (Choi et al., 2006; Scheperjans et al., 2008) also included with FSL. Additionally, the amygdala, dACC, vACC, OFC, were also queried, however they were defined from the automated anatomical labeling (AAL) atlas included in the Wake Forest University Pickatlas toolbox (Tzourio-Mazoyer et al., 2002). These ROIs were defined from an atlas outside of the FSL toolkit due to the increased resolution available with the AAL atlas (e.g. the OFC is broken into superior, middle, and inferior divisions in the AAL atlas, but is a large region encompassing the entire orbital section of the PFC in the Harvard-Oxford Atlas). Featquery outputs both extent of activation and percent signal change, as calculated from voxel-wise parameter estimate values and averaged within the cluster. ROI analyses allow for the investigation of hypothesized group differences using independent t-tests while decreasing the effects of type II-errors that can occur due to the corrections required in whole-brain analyses.

2.4.3. Partial Least Squares Analysis

Spatiotemporal Partial Least Squares (ST-PLS) analysis is a multivariate analytic tool that is used to assess functional networks that discriminate between task conditions or groups (task-PLS) and to identify how nodes in those networks

are functionally connected with one another. More specifically the functional connectivity analysis, which is termed seed-PLS, correlates activity in a specific ROI with brain activity associated with task conditions, thus providing a measure of functional connectivity (McIntosh et al., 2004; McIntosh and Lobaugh, 2004).

A multi-step approach was used for the PLS analysis. First, mean-centering task-PLS was used to identify neural networks that reliably discriminate between task conditions (Target, Eyes, and Target Eyes). A full description of the mathematical basis of these analyses can be found elsewhere (McIntosh et al., 2004; McIntosh and Lobaugh, 2004). Briefly, data from the fMRI time series for each participant are extracted at each voxel (m) across each time point (t). The m and t information is then incorporated into a data matrix (M), containing vectors for each of subject (n) in each condition (k). Then, the matrix (M) is averaged within the task and is subjected to singular value decomposition. The patterns of activity that are derived from a PLS analysis are referred to as “saliencies.” In task-PLS, the salience associated with each voxel describes how that voxel is related to whole-brain activity (brain salience) and to the task design (i.e. differences in activity between conditions, termed design salience). Specifically, if a voxel from a task-PLS analysis has a positive salience then the activity in that voxel is more strongly associated with positive salience task conditions than it is with negative salience task conditions and vice versa for activity in negative salience voxels (Caplan et al., 2007)

Following the mean-centered task-PLS analysis, functional connectivity was assed using seed-PLS, which correlates the task-related functional brain response

with the normalized BOLD response from voxels within a seed of interest. Like in task-PLS, seed-PLS produces saliencies that describe how whole brain activity, as associated with task design, covaries with activity in the seed region. In seed-PLS, activity in positive salience regions is positively covaried with activity in the seed during positive seed salience conditions, and negatively covaried to activity in the seed during negative seed salience conditions. Thus, if activity in the seed increases to positive seed salience condition, activity in the positive salience voxels will also increase. The opposite pattern is found for negative salience voxels. Specifically, activity in negative salience regions is positively covaried to activity in the seed during negative seed salience conditions, and negatively covaried to activity in the seed during positive seed salience conditions (Caplan et al., 2007).

In addition to understanding how brain activity covaries with task design and seed activity, it is also possible to use PLS to identify networks that differentiate between behavioral measures, such as accuracy and reaction time. The behavior saliencies derived from this behavior-PLS analyses are interpreted in the same way as seed saliencies. Specifically, activity in positive salience regions is positively covaried to positive-salience behavioral measures, such as accuracy, and negatively with negative salience behavioral measures, namely being associated with decreased reaction time (Caplan et al., 2007). By pairing behavior-PLS and seed-PLS, it is possible to identify neural networks that are not only associated with activity within a specified seed, but to understand how modulation of the network in relation to the seed contributes to task performance.

All PLS analyses were performed in Matlab version 7.10.0 (Mathworks, Inc) utilizing code that is available for download at http://www.rotman-baycrest.on.ca/index.php?section=345. Prior to running the PLS analysis preprocessed data from the FSL analysis were converted from NIFTI format to ANALYZE format. Following this, all runs for each subject were concatenated to form a single long run and the data were spatially normalized to the standard Montreal Neurologic Institute (MNI) brain.

Each PLS analysis produces a set of latent variables (LVs), which correspond to neural networks that explain patterns in the data, much like the various components in an independent component analysis (ICA). The significance of each PLS LV was determined through 500 iterations of permutation testing, which provides a measure of the likelihood that the LV effect could be associated with random noise. LVs with $p \leq 0.05$ were considered significant. Reliability was assessed via bootstrap estimation of the standard errors for each of the voxel saliencies (100 iterations). A minimum of 50% of different subject numbers was used for the bootstrap estimation. The ratio of the voxel salience to bootstrap estimation is referred to as the bootstrap ratio (BSR). BSRs, which are approximately equivalent to a z-score, provide an estimation of how reliably each data point in the LV contributes to the significance of that LV. Individual saliencies were considered significant if their confidence intervals, as determined through the bootstrap testing, did not include zero. Analyses were not corrected for multiple comparisons, as they are not required for PLS analysis (McIntosh et al., 2004).

Regions that were significantly related to an LV were identified utilizing the cluster report function in the PLS GUI. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels. Anatomical localizations were determined through comparison with the Harvard-Oxford cortical and subcortical probabilistic structural atlases, which are included in the FSL analysis software package. Input for the seed-PLS analysis was derived from task-PLS analyses. Specifically, activity from peak voxels in the each of the seed clusters were extracted from the task-PLS analysis with a cluster neighborhood size of 1 voxel (i.e. each seed cluster was comprised of the peak voxel and each of its surrounding voxels).

2.5. Tables

Measure	High-Functioning Autism (N = 15)	Typically Developing (N = 15)	Group Comparison p-value
Age	27.33 (10.38)	27.60 (6.56)	0.934
WASI			
Verbal IQ	106.00 (17.91)	112.53 (7.38)	0.204
Performance IQ	110.50 (13.44)	117.40 (10.26)	0.130
Full-Scale IQ	109.36 (16.30)	116.60 (8.24)	0.139
ADI-R			
Social	15.54 (4.63)		
Verbal Communication	14.08 (3.82)		
Repetitive Behavior	4.14 (1.4)		
ADOS			
Social	7.20 (2.60)		
Communication	5.33 (3.6)		

Table 2.1. Participant Demographics.

Mean (s.d.) of demographic data from neurotypical and high-functioning autism participants. Group comparisons were analyzed via one-way ANOVA. WASI scores were unavailable for one participant with high-functioning autism. Additionally, there were no informants available for two individuals with autism and therefore ADI-R scores are not included for these participants.

2.6. Figures

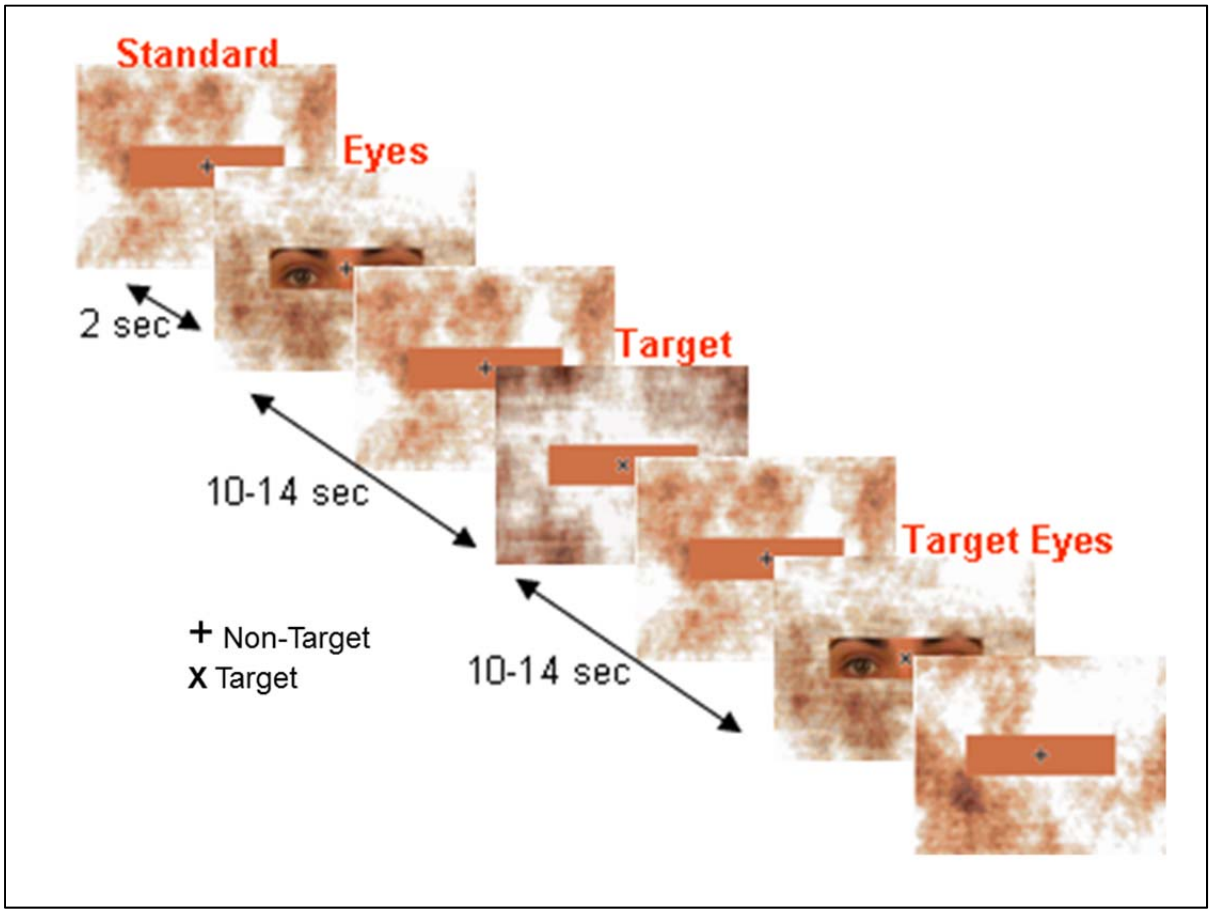

Figure 2.1. Social Target Detection Task.

The Social target Detection Task consisted of eight event-related runs, each containing 124 stimuli from four categories: Standards (88%), Target Alone (Target; 4%), Eyes Alone (Eyes; 4%), and Target plus Eyes (Target Eyes; 4%). Stimuli from each novel condition were presented in random order and were spaced 10-14s apart. All stimuli were presented at jittered interstimulus intervals of 1600-2000ms and each stimulus was presented for. Participants were instructed to indicate whether the central fixation point represented a non-target (+) or a target (X) using a two choice button box.

CHAPTER 3. RESULTS

3.1. Behavioral Performance in Neurotypical Group

Behavioral performance in the neurotypical group was probed in an effort to understand the effect of pairing a task-irrelevant social distracter, namely an image of eyes with direct gaze, on target processing, inhibition of a prepotent response, initiation of a novel motor response, and context-updating. Furthermore, behavioral analyses allowed for the investigation of the hypothesis that neurotypical controls would exhibit the same benefit from pairing an executive task with a socially-relevant context even if the goal-directed behavior was not contingent upon information imparted by the socially-relevant context. Based on previous research, it was hypothesized that the behavioral response to the Eyes Alone condition in the neurotypical controls would be similar to that of the standard stimuli based on the lack of a shift in motor response. It was further hypothesized that behavioral responses to the Target Alone condition would be slower and less accurate than responses to both the Eyes Alone and the Standard stimuli. This was based on the greater requirement for cognitive control involved both in comparing the stimulus to the representation of the target, as well as a need to inhibit the prepotent behavioral response and initiate a novel motor action. Finally, based on the findings from Dichter and colleagues, better accuracy was expected to the Target Eyes as compared to the Target Alone condition in neurotypical controls (Dichter and Belger,

2007; Dichter et al., 2009b). Despite better accuracy, slower reaction times were predicted in this condition because greater cognitive control would be required as the social stimuli would be capturing attention and directing it away from the target stimulus.

Accuracy (percent correct) and latency of correct responses for all conditions are summarized in Figure 3.1. Repeated measure ANOVAs were used to assess differences in both accuracy and latency across all conditions. Mauchly's tests indicated that the assumption of sphericity was violated for both accuracy (χ^2 (5) = 50.98, $p \leq 0.000$) and latency (χ^2 (5) = 15.68, $p < 0.05$), and therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.48$ for accuracy and $\varepsilon = 0.64$ for latency). Repeated measure ANOVA revealed a significant main effect of condition (Standard, Target Alone, Eyes Alone, and Target Eyes) on accuracy ($F(1.44, 17.32) = 31.55$, $P \leq 0.000$). A significant main effect of condition was also seen in the latency of correct responses ($F(1.92, 23.07) = 66.28$, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method. Paired t-tests indicated that there were significant differences in accuracy across all four condition contrasts (Table 3.1) and that there were significant differences in latency between all condition contrasts, with the exception of between Target Alone and Target Eyes (Table 3.2). Specifically, there were significant differences in accuracy between the Standard and Target Alone ($t(12) = 6.94$, $p = 0.000$), Eyes Alone ($t(12) = -2.98$, $p = 0.042$), and Target Eyes ($t(12) = 4.07$, $p = 0.009$) conditions, as well as between the Target Alone and the Eyes Alone ($t(12) = -7.14$, $p = 0.000$) and Target Eyes ($t(12) = -4.40$, p

= 0.006) conditions, and finally between the Eyes Alone and the Target Eyes conditions (t(12) = 4.23, p = 0.007). Additionally, there were significant differences in latency between the Standard and the Target Alone (t(12) = -12,81, p = 0.000), Eyes Alone (t(12) = -4.67, p = 0.003), and Target Eyes (t(12) = -24.90, p = 0.000) conditions, as well as between the Target Alone and Eyes Alone conditions (t(12) = 5.14, p = 0.000), and between the Eyes Alone and the Target Eyes conditions (t(12) = -4.08, p = 0.003).

3.2. Region-Based Functional Neuroimaging Results for Neurotypical Group

Region-based functional neuroimaging analyses permitted the investigation of the neural circuitry underlying the integration of an executive task with an irrelevant social context. Furthermore, it permitted the investigation of the effect this interaction had on the recruitment of attentional resources associated with the Target Eyes condition. Previous research (e.g. Yamasaki et al., 2002) has identified that there are separate, yet connected, neural networks associated with processing executive and social information and these networks often work in opposition to one another (i.e. when the VSAPS network is active it decreases the resources available to the cognitive DECS network and vice-versa). Thus, this analysis allows the investigation of the following questions: 1) what happens to the balance of activation in the DECS and VSAPS neural circuits when an executive task is paired with task-irrelevant social information? 2) Is there any modulation by the DECS/VSAPS on the attention network or vice versa? It was hypothesized that the Eyes Alone condition would activate social networks, as well as the neural circuitry involved in

context updating and processing of task-irrelevant distracter stimuli. The Target Alone condition was anticipated to activate the attention, salience designation, and target detection networks. Finally, it was anticipated that the Target Eyes condition would be associated with preferential activation in the dACC, replicating the Dichter (2009b) results. Additionally, it was projected that there would differential activation of the ventral social and dorsal executive control systems, whereby increased activity in one would be associated with decreased activity in the other.

Main effects were computed on correct trials only (Table 3.3). When the eyes were presented alone, large areas of activation were seen bilaterally in the visual processing stream, including the FFC, which is involved in processing faces (Figure 3.2). When the target was presented alone, there was a robust activation in the dACC, which is important for executive functioning and target processing. There was also activation in the attentional network, specifically bilaterally in the superior parietal cortex, including the right IPS, as well as in the precuneus (Figure 3.2). Finally, there was an apparent additive effect when the target was paired with the eyes, with regions that were active in the Target Alone and the Eyes Alone conditions being activated together. These regions included the areas associated with social processing that were seen in the Eyes Alone condition, namely the large activation in the occipital cortex and FFC, as well as regions associated with target processing such as the dlPFC. There was also greater recruitment of attentional and cognitive control resources when the target was paired with the eyes, with activation seen in the right insula/OFC, as well as in the left frontal operculum cortex, extending into the insula and vlPFC (Figure 3.2).

Regions that were activated more in one condition as compared to another were explored in contrast analyses (Table 3.4). The contrast between the Target Eyes and the Eyes Alone conditions allows for the investigation of the effect of the need to inhibit the prepotent motor response in the presence of a task-irrelevant eye distracter, while controlling for the effect of the eyes on stimulus processing in general. This contrast revealed that there was significantly greater activation in regions involved in attention and cognitive control to the Target Eyes condition, namely the postcentral gyrus and superior parietal cortex in the left hemisphere, and the SMG, including the superior parietal cortex, angular gyrus, and IPS, as well as the putamen extending into the insula in the right hemisphere (Figure 3.3). The contrast of the Target Eyes with the Target Alone condition allows for the dissociation between the effect imparted by the interference by the eyes, which is specific to the Target Eyes condition, and the effect of the need to inhibit the prepotent response, which is the shared between the conditions. This contrast revealed that when the target was paired with eyes there was greater activation in the right occipital FFC and the left lateral occipital cortex, including the bilateral FFC (Figure 3.3). An additional analysis was run to determine which regions were more active in response to the Target Eyes condition as compared to the conjunction of the Eyes and Target conditions, which was termed the "Pure Social Target condition." This contrast identified the unique effect of pairing the task-irrelevant eyes with the target, thus providing information on the effect of the need to both inhibit the task-irrelevant eyes and the prepotent motor response. This contrast revealed that the superior parietal cortex/IPS and the occipital FFC, were more

engaged when the target was paired with the eyes than when either the target or the eyes were presented alone (Figure 3.3). Because of the loss of power associated with doing a multiple condition contrast such as this, an additional uncorrected analysis was run on the Pure Social Target condition. This analysis revealed increased activity in multiple regions, including the right dACC, bilateral dlPFC, right MTG, right angular gyrus, bilateral superior parietal cortex, and right IPS in response to the Target Eyes condition as compared to both the Target Alone and the Eyes Alone condition (Supplementary Table A.1).

3.3. Functional Connectivity Analysis for Neurotypical Group

Functional Connectivity analyses were implemented in order to explore the functional networks that differentiate between conditions (as opposed to activate in each condition), are associated with differential performance on the task, and are related to activity in specific structures in relation to the conditions. Specifically, this analysis set out to address the following questions: 1) what are the network level patterns of activity that are associated with processing the paired target and distracter information, 2) how does activity in regions at the interface of the DECS and VSAPS (i.e. dlPFC, vlPFC, OFC) modulate activity in the rest of the brain, and 3) How does this network level activity influence behavioral performance? It was expected that there would be significant reciprocal correlations between the dorsal executive and ventral social affective processing systems in the functional connectivity analyses in the neurotypical control group and that the direction of these correlations would be associated with differential behavioral output (i.e. RT).

3.3.1. Task-PLS in Neurotypical Controls

Mean-centering task-PLS was used to identify neural networks that were differentially engaged in response to the task conditions. This analysis identified a single latent variable (LV1) that described 58.02% of the crossblock covariance and was associated with a neural network, which reliably ($p < 0.026$ by permutation test) discriminated between social and executive processes. This LV was associated with a positive salience network that was differentially involved in processing the Target Alone condition and a negative salience network involved in processing the Eyes Alone and the Target Eyes conditions (Supplementary Tables Table A.2Table A.3 and Supplementary Figure B.1-Figure B.2). Regions with positive salience were driven by the target when it was presented by itself and included regions known to be involved in cognitive control and attention, such as the anterior angular gyrus (PGa), superior parietal cortex, posterior MTG (pMTG), and vmPFC in the right hemisphere, the IPS (hIP2), anterior MTG (aMTG), and basal ganglia (BG) in the left hemisphere, and bilateral dACC and PCC. Activity in the negative salience network contributed more to the social conditions, especially the Target Eyes condition. This network also included activations in executive and attentional regions, including bilateral PCC, BG, and pMTG, as well as left aMTG and superior parietal cortex. Additionally, there was activation in regions important for social processing, namely bilateral FFC, as well as additional recruitment of regions known to be involved in regulating attention to social/emotional information and its integration with executive processes, such as the right dACC, vACC, rACC, bilateral vmPFC, dmPFC and SFG, and the left thalamus. Finally, regions that lie at the interface of the VSAPS

and DECS, such as the OFC, vlPFC, and dlPFC were associated with activity in both networks, but with some differential hemispheric distributions.

3.3.2. Seed-PLS in Neurotypical Controls

Right OFC (44, 28,-8), left vlPFC (-48, 20, 14) , and right dlPFC (40, 8, 24) seeds were chosen from the mean-centering PLS results for the functional connectivity analysis based on their overlap with activations found in the region-based FSL analysis (Supplementary Table A.4), as well as their known role in integrating social/emotional and executive processes. For each seed analysis, intensity values from the lag where the seed had the highest BSR was extracted from the task-PLS analysis and fed into the design along with the z-score transformed reaction time (RT) for each subject. RT was investigated as opposed to the accuracy due to the use of correct only trials, which ensures that analyses only included trials in which participants had attended to the stimulus. This analysis outputs functional neural networks that are associated with task-related brain activity and describes how that activity is related to activity in the seed of interest, as well as the effect that differential activation of the networks have on behavioral responses.

The first seed-PLS analysis explored the neural circuitry that interacts with a cluster located in the right OFC and the effects of this interaction on RT to the three task conditions. This analysis identified a significant LV that explained 27.24% of the crossblock covariance ($P < 0.01$ by permutation testing) and that showed a differential pattern of activation based on the presence or absence of a target stimulus, namely with Target and Target Eyes conditions as compared to the Eyes Alone condition (Figure 3.4, Supplementary Figure B.3). There was no negative

salience network associated with this LV; however there was a positive salience network where increased activity in the network was associated with increased activity of the right OFC to Targets and Target Eyes and decreased activity of the right OFC to Eyes. Additionally, this neural network was positively correlated with RT to the Target Eyes and negatively correlated with RT to the Eyes, suggesting that when activity in the positive network increased along with the right OFC it was associated with slower (i.e. worse) RTs to the Target Eyes. Conversely, when activity in the positive network increased to the Eyes Alone condition, activity in the OFC decreased and this was correlated with faster (i.e. better) RTs to the Eyes Alone. While this network was activated in response to the target stimuli, the RT to the targets was independent of the level and direction of activations in the network. Regions that were identified in the positive salience neural network included regions involved in social processing, including the left amygdala and the right hippocampus, as well as right-lateralized regions that are involved in attention allocation, such as the PCC, IPS (hIP1), and the pulvinar and medial dorsal (MD) nuclei of the thalamus. In addition, there was a large contribution of regions involved in cognitive control, attention allocation, and the integration of executive and social information. This included bilateral dACC, rACC, vACC, and vlPFC, as well as left dlPFC, dmPFC, OFC, insula, and right vmPFC (Figure 3.5 ,Supplementary Table A.5).

The seed-PLS analysis investigating functional connections to the left vlPFC and the effect of this network on RT identified a significant LV that explained 21.06% of the crossblock covariance ($p < 0.046$ by permutation testing). The positive salience network associated with this LV displayed a positive correlation with the

vlPFC to the Target Eyes condition and a negative correlation with the Target and Eyes conditions (Figure 3.4, Supplementary Figure B.4). Thus, when activity in the positive salience network increased to the Target Eyes, activity in the left vlPFC also increased, but as activity in this network increased to the Target or the Eyes Alone conditions, activity in the left vlPFC decreased. In addition, the positive salience network showed a positive correlation with RT to the Target Eyes, while being independent to the RT to both the Target and Eye conditions. Therefore, when activity increased in the positive salience network in response to the Target Eyes condition, activity in the left vlPFC also increased, and this was associated with increased (i.e. slower) RTs to the Target Eyes condition. The opposite pattern of activity would be expected when activity in the positive salience network decreased. This LV also identified a negative salience network which displays the opposite connectivity patterns. Specifically, increased activity in the negative salience network was associated with increased activity in the left vlPFC to the Target and Eyes conditions, but was correlated with decreased activity in the left vlPFC to the Target Eyes condition and this pattern of activation was associated with better RTs to the Target Eyes. Regions in the positive salience network included many of the same regions as were identified in the right OFC seed analysis, including regions at the interface of the VSAPS and the DECS, namely the dACC, rACC, vACC, left dlPFC, right OFC, Left vlPFC, bilateral vmPFC. In addition, there was activation in social processing regions, including the right hippocampus and right parahippocampal gyrus, as well as in attention processing regions such as the bilateral posterior cingulate, right superior parietal cortex, and bilateral precuneus

cortex. The negative salience network was comprised of mostly sensory-motor processing regions, though there was activation in the bilateral OFC, vlPFC, and insula, as well as in the attention network comprised of the anterior IPS, PCC, and the pulvinar nucleus of the thalamus (Figure 3.6, Supplementary Table A.6Table A.7).

The final seed-PLS analysis explored the neural networks functionally coupled to the right dlPFC and how activity in these networks relates to RT to the task. This analysis identified a significant LV that explained 24.55% of the crossblock covariance ($p < 0.006$ by permutation test). The positive salience neural network associated with this LV identified regions that when activated were associated with decreased activity in the right dlPFC to the Target and Target Eyes condition, but that was independent of activity in the right dlPFC to the Eyes Alone condition. Furthermore, activation of this network and the subsequent decrease in right dlPFC activity was associated with slower RTs to the Eyes and Target Eyes conditions, while being independent of RT to the Targets (Figure 3.4, Supplementary Figure B.5). Again, the opposite pattern would be expected with decreased activity in the negative salience neural network. Regions identified in this positive salience neural network included many of the same regions identified in the right OFC and left vlPFC seed-PLS analyses, including the dACC, vACC, bilateral OFC, left vlPFC, right vmPFC, bilateral hippocampus, right parahippocampus, and the right superior parietal cortex. In addition to these regions, the positive salience network included the right amygdala and the left FFC, both of which are important for social processing. The negative salience neural network identified by this LV was similar

to the negative salience network from the left vlPFC analysis, and included regions such as the rACC, vACC, left dlPFC, bilateral OFC, right vmPFC, insular cortex, and superior parietal lobule, including the intraparietal sulcus. Increased activity in this negative salience network was associated with increased activity in the right dlPFC to Targets and Targets Eyes and faster RTs to the Eyes Alone and Target Eyes conditions (Figure 3.7, Supplementary Table A.8Table A.9).

3.3.3. Overlapping networks within seed-PLS analyses in Neurotypical Controls

Overlapping regions from each of the three seed-PLS analyses were identified in an effort to uncover a unified model of functional connectivity to the Target Eyes condition. This was accomplished by identifying clusters with overlapping voxels that were activated in two or more of the seed-PLS analyses. Only those regions that have identified roles in cognitive control, attention, social processing, and the interaction of these cognitive domains were queried for this exploratory analysis. Many regions showed overlap between the positive neural networks from the left vlPFC seed-analysis and the right OFC and right dlPFC analyses. Namely, there was overlap between the right dlPFC and the left vlPFC analyses in the vmPFC and the right OFC (medial to the right OFC seed). Additionally, there was overlap between the left vlPFC and the right OFC analyses in the right dACC, right vACC, and the left rACC. Finally, a cluster in the right posterior cingulate was shared across all three seed-PLS analyses. A list of the regions with overlapping voxels, including the MNI-coordinates of the overlap , as well as the BSR and seed/RT correlation values are outlined in Table 3.5. Together, the overlap in these regions suggests that this task modulates a neural network whereby

increased activity in the VSAPS, including the bilateral hippocampi, bilateral amygdala, and the vmPFC was associated with increased activity in regions at the interface of the VSAPs and the DECS, such as the right OFC, left vlPFC, as well as the rACC, vACC, and dACC. Increased activity in this network was also correlated with increased activity in the right posterior cingulate, the anterior IPS, and the right pulvinar nucleus of the thalamus, all of which are associated with the allocation of attentionial resources. Furthermore, increased activation in this entire network was associated with decreased activity in the right dlPFC and this collective pattern of activity results in slower RTs to the Target Eyes. On the other hand, when activity in the right dlPFC increased to the Target Eyes, activity in the rest of the network decreased and this was correlated with faster RTs to the Target Eyes (Figure 3.8). The dlPFC and vlPFC negative salience networks exhibited no overlap with one another, nor was there any overlap between the vlPFC negative network and the OFC positive network.

3.4. Behavioral Performance in Individuals with High-Functioning Autism and Comparison to Neurotypical Controls

Behavioral performance was probed in an effort to understand whether individuals with autism display a similar behavioral benefit to pairing the executive information with a task-irrelevant social context. Based on research and the theory that social stimuli may increase arousal in individuals with autism (Dalton et al., 2005), it was expected that reaction time to the Eyes Alone condition would be slower than that of neurotypical controls. Furthermore, it was anticipated that

deficits in cognitive flexibility and inhibition of prepotent response would result in decreased accuracy and slower reaction time to the Target Alone condition in the group with autism. Finally, it was hypothesized that individuals with autism would not show the same behavioral benefit as the neurotypical controls to having a social stimulus paired with the cognitive task. Instead, it was expected that individuals with autism would have equal or slightly worse accuracy to the Target Eyes condition as compared to the Target Alone condition and that this would be associated with slower reaction times to Target Eyes.

Accuracy and latency of correct responses for the individuals with high-functioning autism are summarized in Figure 3.9. Repeated measure ANOVAs were used to assess differences in both accuracy and latency across all conditions. Mauchly's tests indicated that the assumption of sphericity was violated by both accuracy (χ^2 (5) = 22.43, $p \leq 0.000$) and latency (χ^2 (5) = 26.40, $p \leq 0.000$), and therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.47$ for accuracy and $\varepsilon = 0.48$ for latency). Repeated measure ANOVA revealed a significant main effect of condition (Standard, Target Alone, Eyes Alone, and Target Eyes) on accuracy (F (1.41, 18.27) = 46.14, $P \leq 0.000$). A significant main effect of condition was also seen in the latency of correct responses (F (1.45, 18.82) = 66.92, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method. Paired t-tests indicated that there were significant differences in accuracy across all condition contrasts, with the exception of between the Eyes Alone and Standard conditions (Table 3.6) and that there were significant differences in latency between

all condition contrasts, with the exception of between Target Alone and the Target Eyes conditions (Table 3.7). Specifically, there were significant differences in accuracy between the Standard and Target Alone ($t(13) = 8.34$, $p = 0.000$) and Target Eyes ($t(13) = 6.46$, $p = 0.000$) conditions, as well as between the Target Alone and the Eyes Alone ($t(13) = -7.42$, $p = 0.000$) and Target Eyes ($t(13) = -4.09$, $p = 0.008$), and finally between the Eyes Alone and Target Eyes conditions ($t(13) = 5.65$, $p = 0.000$). Additionally, there were significant differences in latency between the Standard and the Target Alone ($t(13) = -9.95$, $p = 0.000$), Eyes Alone ($t(13) = -4.60$, $p = 0.003$) and Target Eyes ($t(13) = -11.97$, $p = 0.000$) conditions, as well as between the Target Alone and Eyes Alone ($t(13) = 6.52$, $p = 0.000$), and between the Eyes Alone and the Target Eyes conditions ($t(13) = -6.65$, $p = 0.000$).

Between group analyses of accuracy (percent correct) and latency of correct responses for all conditions are summarized in Figure 3.10. Differences in accuracy and latency were assessed via 2(Group) x 4(Condition) repeated measure ANOVAs. Mauchly's tests indicated that the assumption of sphericity was violated by both accuracy (χ^2 (5) = 52.04, $p \leq 0.000$) and latency (χ^2 (5) = 37.71, $p \leq 0.000$), and therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.47$ for accuracy and $\varepsilon = 0.60$ for latency). Repeated measure ANOVA revealed a significant main effect of condition on accuracy ($F(1.42, 37.00) = 80.20$, $P \leq 0.000$). There was a significant group by condition interaction on accuracy, but it did not survive the more stringent Greenhouse-Geisser correction, however there was still a trend for an interaction ($F(1.42, 37.00) = 2.86$, $p = 0.086$). This analysis was followed up with independent-samples t-tests because there was

a significant interaction prior to the Greenhouse-Geisser correction despite there only being a trend with the correction. The independent-samples t-tests revealed that the group by condition interaction was being driven by a significant between group difference on accuracy to the Target Eyes condition ($t(26) = -2.124$, $p = 0.043$). A significant main effect of condition was also seen in the latency of correct responses ($F(1.80, 46.58) = 127.02$, $P \leq 0.000$) and there was a significant group by condition interaction ($F(1.8, 46.58) = 4.25$, $p = 0.024$). Independent-samples t-tests, however, revealed no significant between group differences for any of the conditions.

An additional analysis was run to investigate the ability of individuals with autism and neurotypical controls to discriminate (d') between the Eyes Alone and the Target Eyes conditions. In this study, the d' was used to a measure how well individuals were able to filter the "noise" introduced into the target processing system by the task-irrelevant eye stimuli. Specifically, it was calculated by taking the absolute value of the subtraction of the z-score transformed false alarm rate to the Eyes Alone condition from the z-score transformed hit rate to the targets in the Target Eyes condition (i.e. d' = |Z(Hit to Target Eyes)-Z(False Alarms to Eyes Alone)|). Independent samples t-tests revealed that individuals with autism were significantly worse than neurotypical controls ($t(26) = -2.88$, $p = 0.008$) at discriminating between the non-target Eyes alone condition and the Target Eyes condition (Figure 3.11).

3.5. Region-Based Functional Neuroimaging Results for Participants with High-Functioning Autism

Just as in the analysis for the neurotypical group, main effects were computed on correct trials only (Table 3.8Table 3.9, Figure 3.12). When the eyes were presented alone, the individuals with autism displayed similar activations to that seen in the neurotypical group, namely with bilateral activation of the FFC. When the targets were presented alone, individuals with autism also displayed activation in many of the same regions as neurotypical participants, including the right supplementary motor cortex extending into the dACC, as well as bilateral superior parietal regions including the right IPS. When the target was paired with the eyes, individuals with autism recruit a broader network than that seen in the neurotypical group. This network included the parietal cortex and intraparietal sulcus, as well as the dlPFC, insular cortex, and cerebellum in the right hemisphere. Additionally, in the left hemisphere there was a large activation in the precentral gyrus extending into the dlPFC, as well as the lentiform nucleus of the putamen, the postcentral gyrus extending into IPS, and the OFC extending in to the insula.

Contrast analyses in the high-functioning autism group revealed that any differences in the activation between the Target Alone condition and the Target Eyes condition did not survive correction. There was, however, greater activation of the left superior parietal cortex, as well as the pre- and post-central gyri in the Target Eyes condition than in the Eyes Alone condition. Additionally, there was increased activity in the left postcentral gyrus, extending into the precentral gyrus and the posterior IPS in the Pure Social Target condition that was corrected for multiple

comparisons. The uncorrected analysis of the Pure Social Target Condition revealed activations in sensory and extrastriate regions, such as the lateral occipital cortex and lingual gyrus, as well as in the postcentral gyrus in the left hemisphere. There was also activation in sensory and extrastriate regions of the right hemisphere, namely the occipital pole. Additionally there was increased activation of the right insula and right superior parietal cortex, including the IPS, as well as of midline dACC in the Target Eyes as compared to the combination of the Eyes Alone and Target Alone conditions (Table 3.10, Figure 3.13, Supplementary Table A.10).

3.6. Region-Based Functional Analysis of Between Group Effects

Comparing the region-based functional neuroimaging analyses in the individuals with autism to the neurotypical control group permitted the investigation of how the neural circuitry underlying the integration of an executive task with an irrelevant social context was differentially regulated in the individuals with autism. It was anticipated that individuals with autism would activate FFC to an equal extent in the Eyes Alone condition to that seen in neurotypical controls because the short stimulus duration and the placement of the target between the eyes facilitates foveation of the social stimulus. Additionally, if the Dalton (2005) theory of eye processing is correct, it was predicted that there would be increased amygdala activation to the Eyes Alone in individuals with autism. Based on previous research with the oddball task in autism, it was anticipated that the Target Alone condition would be associated with decreased activation in cognitive control neural networks, specifically in the dlPFC, ACC, and IPS. Finally, it was projected that the Target

Eyes condition would be associated with increased activity in the ventral social affective system, which would interfere with cognitive processing and thus result in decreased activity in dorsal attentional and executive control networks.

Between group analyses revealed that while there seemed to be a broader network of regions activated to the Target Eyes condition in the individuals with autism as compared to neurotypical controls, none of these regions survived the contrast analysis. In the Eyes Alone condition, however, the individuals with autism activated a number of regions more than the neurotypical group, specifically showing greater activation in the right FFC extending rostrally into the parahippocampal gyrus, as well as the right dmPFC and caudate (Figure 3.14, Table 3.11). In the Target Alone condition, neurotypical controls activated the right lateral occipital cortex more than individuals with high-functioning autism (Figure 3.15, Table 3.12).

In addition to investigating the between group differences on each condition, an uncorrected analysis was completed examining group differences within the condition contrasts. The first group by condition contrast identified regions where the difference between the Target Eyes condition and the Eyes Alone condition was larger for one group compared to the other, there was increased activation of right lateralized putamen, dmPFC, precuneus, and MTG in the neurotypical participants as compared to the individuals with high-functioning autism (Figure 3.15, Table 3.12). The second group by condition contrasts investigated regions where the Target Eyes condition activated more than the Target Alone condition and identified that individuals with autism activated the right SFG more in the Target Eyes condition than in the Target Alone condition as compared to the neurotypical

controls (Figure 3.14, Table 3.11). Finally, in the Pure Social Target condition contrast, the individuals with autism activated the left SFG, SMG, and right angular gyrus more than did the neurotypical controls (Figure 3.14, Table 3.11). On the other hand, the neurotypical group activated left lateralized superior parietal cortex, FFC, STG, as well as insular and extrastriate cortices more than the individuals with high-functioning autism. The neurotypical group also displayed greater activation in the right MTG and precentral gyrus in this group by condition contrast (Figure 3.15, Table 3.12).

Additional region of interest (ROI) analyses were run in an effort to detect between group differences that may be lost due to the increased statistical limits placed on whole brain analyses due to a need to correct for multiple comparisons (Figure 3.16). The regions were chosen a priori due to their role in social processing, cognitive control, and attention, and were defined anatomically. In the Eyes Alone condition, there were significant differences in the extent of activation in the dACC ($t(26) = 2.551$, $p = 0.017$), right occipital FFC ($t(26) = 2.650$, $p = 0.014$), and PCC ($t(26) = 2.229$, $p = 0.035$), with individuals with autism activating larger areas within these regions than neurotypical controls. In the Target Alone condition, the only ROI to show a significant difference was the right posterior IPS (hIP3), which was activated to a greater degree, as measured by percent signal change, in neurotypical controls than individuals with autism ($t(26) = -2.239$, $p = 0.034$). Finally, in the Target Eyes condition, the only region to show between group activation differences was the left inferior OFC, of which the extent of activation was larger in

the individuals with autism as compared to the neurotypical controls ($t(26) = 2.320$, $p = 0.028$).

3.7. Comparison of Functional Connectivity between Individuals with High-Functioning Autism and Neurotypical Controls

3.7.1. Between Group Task-PLS

Mean-centering task-PLS was used to identify neural networks that were differentially engaged in response to the task conditions in both the neurotypical and the high-functioning autism groups. Finally, there is a hypothesis that autism is characterized by local over-connectivity and long-range under-connectivity, with fronto-parietal, fronto-temporal, and fronto-limbic connections being especially aberrant (Geschwind and Levitt, 2007). Thus, it was hypothesized that functional connectivity analyses of activation to the Target Eyes condition in individuals with autism would reveal decreased long-range connections between fronto-parietal, fronto-temporal, and fronto-limbic systems. Additionally, it was believed that disconnection in these networks would be associated with the inability of individuals with autism to exert top-down attentional and cognitive control over the task-irrelevant social context.

Data from one additional participant with high-functioning autism was discarded for this analysis due to severe skewing of the data (Supplementary Figure B.6). The reanalysis of the data with this participant removed identified a latent variable (LV1) that described 35.59% of the crossblock covariance ($p < 0.006$ by permutation test) and was associated with a similar neural network to the one that

discriminated between social and executive processes in the analysis of the neurotypical group alone. Specifically, this LV was associated with a positive salience network that was differentially involved in processing the Target Alone condition and a negative salience network primarily involved in processing the Target Eyes condition in both groups, however the level of discrimination in the individuals with autism as nearly double that of the neurotypical group (Supplementary Table A.11, Supplementary Figure B.7). Regions with positive salience were activated by the target when it was presented by itself and included regions involved in cognitive control and attention, such as the bilateral BG, rACC, PCC, vlPFC, right insula, left IPS (hIP3), right superior parietal cortex, right pMTG, and the pulvinar nucleus of the right thalamus. Additionally, there was activation in the left amygdala, which may have been responding to the salience of the target stimulus, as well as the hippocampus, which was involved in memory and has been demonstrated to be a "source" of neural activity for the generation of the P300 evoked response to targets, and therefore represents an important node for target detection. Activity in the negative salience network contributed more to the Target Eyes condition in individuals with high-functioning autism. This network also included activations in executive and attentional regions, including the bilateral PCC, the dACC and IPS (hIP1 and hIP3) in the left hemisphere, and the superior parietal cortex, pITG, and pMTG in the right hemisphere. Finally, regions that lie at the interface of the VSAPS and DECS, such as the vACC, dlPFC, OFC, and vmPFC were associated with activity in both networks, but with some differential hemispheric distributions (Supplementary Figure B.8).

3.7.2. Seed-PLS Comparing Individuals with Autism to Neurotypical Controls

Functional connectivity in the individuals with high-functioning autism was investigated through seed-PLS analysis of the dlPFC and OFC seeds queried in the neurotypical participants (Supplementary Table A.4). The vlPFC seed was not incorporated in this analysis because there was no comparable vlPFC region from the between group task-PLS analysis and thus there was no voxel intensity information available for extraction. Just as in the seed-PLS from the neurotypical participants, intensity values from the lag where the seed had the highest BSR was fed into the design along with the z-score transformed reaction time (RT) for each subject with high-functioning autism.

The first seed-PLS analysis explored the neural circuitry that interacts with a cluster located in the right OFC and the effects of this interaction on RT to the three task conditions. This analysis identified a LV that was negatively correlated to activity in the right OFC in all three conditions (53.40% of the crossblock covariance $P < 0.000$). Specifically, increased activation in the positive salience neural network of LV1 in the right OFC seed-PLS analysis was associated with decreased activation in the right OFC to the Target Alone, Eyes Alone and Target Eyes conditions. This network was also positively correlated with RT to the Target Alone and the Target Eyes conditions, such that increased activity in the network was associated with slowed RT to targets (Figure 3.17, Supplementary Figure B.9). The positive salience network was comprised of regions associated with social processing, such as the right FFC, as well as with integrating social and cognitive information, namely the dACC, right dmPFC, right dlPFC, and left vmPFC. There was an additional

activation left insula. The negative salience network, which was associated with increased activity in the right OFC and faster RTs, was also comprised of regions important for social processing, specifically the left amygdala, and left FFC. Additional activations were found in the vACC, right dlPFC, right vmPFC, and left hippocampus (Figure 3.18, Supplementary Table A.12).

Functional connectivity in the individuals with autism was also probed for a seed within the right dlPFC. This seed-PLS analysis revealed a single significant LV that accounted for 40.87% of the crossblock covariance ($p < 0.000$ by permutation testing). Increased activity in the positive salience network identified in this LV was associated with increased activity in the dlPFC to the Target Eyes condition, but was independent of dlPFC activity in the Target and Eyes Alone conditions. Increased activity in this network was also associated with worse RT to all three conditions. On the other hand, increased activity in the negative salience network was associated with decreased activity in the dlPFC seed to the Target Eyes condition and faster RTs to all three conditions (Figure 3.17, Supplementary Figure B.10). The positive salience network associated with the right dlPFC included regions involved in social processing, namely the FFC and the right amygdala. Additionally, the positive salience network identified functional connectivity between the right dlPFC and the dACC, dmPFC, dlPFC, and vmPFC, all of which are important for integrating social and cognitive processing, as well as the anterior IPS and insula, which are involved in attentional and cognitive control. The negative salience network included several of the same regions, such as the FFC, dlPFC, dmPFC, dACC, insula and anterior IPS. In addition, the dlPFC was further connected with the left amygdala,

hippocampus, vACC, PCC, vlPFC, and OFC in the negative salience network (Figure 3.19).

3.7.3. Overlapping networks within seed-PLS analyses in Individuals with High-Functioning Autism

Overlapping regions from the right OFC and right dlPFC seed-PLS analyses were identified in an effort to uncover a unified model of functional connectivity with a focus on the Target Eyes condition. Identical to the overlap analysis in the neurotypical participants, this was accomplished by identifying clusters with overlapping voxels that were activated in both of the seed-PLS analyses. Only those regions that have identified roles in cognitive control, attention, social processing, and the interaction of these cognitive domains were queried for this exploratory analysis. Regions that showed overlap between the right OFC and right dlPFC functional networks in the individuals with autism included the amygdala and hippocampus, as well as the dACC, vACC, and PCC (Figure 3.20). No other regions of interests displayed any overlap in the functional networks. A list of the regions with overlapping voxels, including the MNI-coordinates of the location of overlap, as well as the BSR and seed/RT correlation values are outlined in Table 3.13. The pattern of functional connectivity between the dlPFC and the OFC in the individuals with autism suggests that when activity in the network comprised of the PCC, vACC, amygdala, and hippocampus, increased to the Target Eyes condition, activity in the right OFC also increased, whereas activity in the right dlPFC decreased. Additionally, the dACC was differentially regulated by these regions, whereby its activity decreased when activity in the rest of the network increased and

this was correlated with increased activity in the right OFC and decreased activity in the right dlPFC. With respect to behavioral performance, increased activity in the OFC seed and related increased in PCC, vACC, amygdala, and hippocampus were associated with faster reaction time. Additionally, decreased activity in the dlPFC and dACC were also associated with faster reaction time. The opposite patterns would be expected to be associated with slower reaction time.

Interestingly, when comparing the networks identified in the individuals with autism to those identified in neurotypical controls, three main findings emerge. The first was that the left vlPFC seed that was queried in the neurotypical participants was not involved in the network engaged by the individuals with autism. This was not surprising given the results from the region-based fMRI analysis, in which there was clear vlPFC activation in the Target Eyes condition in the neurotypical participants, but no such activation was found in the individuals with high-functioning autism. The second primary finding was that in the neurotypical participants, there was only a single direction of functional connections with the right OFC. Specifically, there was no negative salience neural network, so all regions in the network identified in the neurotypical participants were positively correlated with the right OFC in this group. In the individuals with autism, however, there was both a positive and a negative network associated with activity in the right OFC. The final finding was that there were more nodes displaying overlap between the right OFC and right dlPFC in the individuals with high-functioning autism than in the neurotypical controls (Figure 3.20). Specifically, both groups display overlap between the dlPFC and OFC networks at the PCC, however no other node overlaps between these networks in

the neurotypical controls. On the other hand, the functional networks in the individuals with autism have additional overlapping clusters in the dACC, vACC, amygdala, and hippocampus. However, if the vlPFC connectivity was taken into account when comparing the regions that overlap in the neurotypical participants to that of the individuals with autism, there was striking overlap between the two networks. Specifically, in the individuals with autism there was overlap between seeds in the dlPFC and OFC with activation in the dACC, and vACC, and while these nodes do not overlap between the dlPFC and OFC seeds in the neurotypical participants, they do overlap between the OFC and vlPFC seed analyses. However, there was no equivalent overlap in the neurotypical network to that seen between the OFC and dlPFC in the amygdala and hippocampus of individuals with autism.

3.8. Tables

(I) Accuracy Condition 1	(J) Accuracy Condition 2	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Target	Eyes	-34.769*	4.900	.000	-50.219	-19.320
	Target Eyes	-13.692*	3.159	.006	-23.652	-3.733
	Standard	-33.615*	4.847	.000	-48.897	-18.334
Eyes	Target	34.769*	4.900	.000	19.320	50.219
	Target Eyes	21.077*	5.011	.007	5.279	36.874
	Standard	1.154*	.355	.042	.034	2.274
Target Eyes	Target	13.692*	3.159	.006	3.733	23.652
	Eyes	-21.077*	5.011	.007	-36.874	-5.279
	Standard	-19.923*	4.905	.009	-35.386	-4.460
Standard	Target	33.615*	4.847	.000	18.334	48.897
	Eyes	-1.154*	.355	.042	-2.274	-.034
	Target Eyes	19.923*	4.905	.009	4.460	35.386

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 3.1. Pairwise Comparisons of Percent Correct Responses on Social Target Detection Task in Neurotypical Participants.

Repeated measure ANOVA revealed a significant main effect of condition on average accuracy (% correct responses) in the neurotypical participants ($F(1.44, 17.32) = 31.55$, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method.

(I) Latency Condition 1	(J) Latency Condition 2	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Target	Eyes	76.787*	12.966	.000	35.910	117.664
	Target Eyes	10.409	8.484	1.000	-16.338	37.156
	Standard	142.746*	11.142	.000	107.619	177.873
Eyes	Target	-76.787*	12.966	.000	-117.664	-35.910
	Target Eyes	-66.378*	14.191	.003	-111.117	-21.639
	Standard	65.959*	14.163	.003	21.308	110.610
Target Eyes	Target	-10.409	8.484	1.000	-37.156	16.338
	Eyes	66.378*	14.191	.003	21.639	111.117
	Standard	132.337*	5.315	.000	115.581	149.093
Standard	Target	-142.746*	11.142	.000	-177.873	-107.619
	Eyes	-65.959*	14.163	.003	-110.610	-21.308
	Target Eyes	-132.337*	5.315	.000	-149.093	-115.581

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 3.2. Pairwise Comparisons of Latency to Correct Responses on Social Target Detection Task in Neurotypical participants.

Repeated measure ANOVA revealed a significant main effect of condition on latency of correct responses in the neurotypical participants ($F(1.92, 23.07) = 66.28$, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method.

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Eyes								
Occipital Fusiform Gyrus	R	18	20	-78	-14	4.55	2.09E-06	1068
Lateral Occipital Cortex, inferior division	R	19	38	-78	-10	4.29		
Lateral Occipital Cortex, inferior division	R	18	28	-86	4	3.56		
Temporal Occipital Fusiform Cortex (FFA)	R	37	44	-60	-14	4.01		
Temporal Occipital Fusiform Cortex (FFA)	L	37	-42	-60	-16	4.59	0.000382	608
Occipital Fusiform Gyrus	L	19	-36	-66	-14	4.05		
Temporal Fusiform Cortex, posterior division	L	20	-34	-42	-20	3.14		
Lateral Occipital Cortex, inferior	L	19	-44	-70	-18	3.10		
Target								
Superior Parietal Lobule	L	40	-46	-38	54	4.21	9.06E-06	1126
Supramarginal Gyrus, anterior division	L	40	-44	-34	44	4.03		
Postcentral Gyrus	L	40	-34	-34	42	3.53		
Postcentral Gyrus	L	2	-50	-20	36	3.50		
Lateral Occipital Cortex, superior division	R	7	34	-66	50	3.90	6.79E-05	906
Lateral Occipital Cortex, superior division	R	19	30	-64	40	3.83		
Posterior Intraparietal Sulcus (hIP3)	R	40	38	-50	54	3.56		
Lateral Occipital Cortex, superior division	R	40	44	-58	52	3.39		
Anterior Cingulate Gyrus, dorsal	L	24	-2	12	36	3.67	0.000281	761
Paracingulate	R	32	8	28	34	3.50		
Anterior Cingulate Gyru, dorsal	R	32	10	34	20	3.41		
Precuneus	R	7	6	-70	38	3.52	0.0233	367
Lateral Occipital Cortex, superior division	R	7	-16	-64	46	3.15		
Target Eyes								
Occipital Fusiform Gyrus	R	18	28	-76	-14	4.90	3.86E-38	7803
Temporal Occipital Fusiform Cortex (FFA)	L	37	-40	-60	-16	4.71		
Lateral Occipital Cortex, inferior division	L	18	-38	-80	-14	4.38		
Intraparietal Sulcus, posterior division (hIP3)	R	7	34	-58	48	4.68	1.61E-15	2145
Intraparietal Sulcus, posterior division (hIP3)	R	7	28	-50	40	4.41		
Supplementary Motor Area	L	6	-8	-4	54	3.90	1.70E-08	938
Paracingulate	R	32	8	24	38	3.74		
Supplementary Motor Area	R	6	2	2	54	3.55		
Dorsolateral Prefrontal Cortex	R	9	48	14	28	4.40	2.98E-07	766
Precentral Gyrus	R	9	42	6	32	4.11		
Dorsolateral Prefrontal Cortex	R	44	48	10	22	3.39		
Middle Frontal Gyrus	R	6	44	6	42	3.28		
Insular Cortex	R	47	34	20	-2	3.86	0.00765	244
Orbital Frontal Cortex	R	47	34	28	-6	3.64		
Frontal Operculum Cortex	R	13	36	20	10	3.15		
Insular Cortex	R	13	38	16	-10	2.79		
Frontal Operculum Cortex	L	13	-42	18	0	3.45	0.00865	239
Insular Cortex	L	13	-36	16	2	3.33		
Ventrolateral Prefrontal Cortex	L	*	-50	12	0	3.16		

Table 3.3. Foci of Activation from Main Effects Analysis in the Neurotypical Group

Regions showing a main effect for condition were identified through a mixed effects analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.3$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels.

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Target Eyes > Eyes								
Postcentral Gyrus	L	2	-54	-24	42	3.55	1.24E-12	6315
Postcentral Gyrus	L	40	-36	-32	46	3.47		
Precentral Gyrus	L	6	-28	-20	64	3.48		
Superior Parietal Cortex	L	40	-36	-42	56	3.48		
Supramarginal Gyrus, anterior division	R	40	50	-34	52	3.24	1.14E-05	2223
Superior Parietal Cortex	R	7	26	-52	58	3.18		
Angular Gyrus	R	40	48	-46	44	3.11		
Intraparietal Sulcus, anterior division (hIP2)	R	40	38	-44	46	2.98		
Putamen	R	N/A	22	12	-2	3.40	0.0103	965
Insular Cortex	R	13	38	16	-10	2.87		
Target Eyes > Target								
Occipital Fusiform Gyrus	R	18	28	-74	-14	4.13	0.0023	1496
Occipital Fusiform Gyrus	R	19	36	-68	-14	3.45		
Temporal Occipital Fusiform Cortex (FFA)	R	37	36	-62	-18	3.11		
Lateral Occipital Cortex, superior division	L	19	-34	-76	16	3.36	0.0031	1432
Temporal Occipital Fusiform Cortex (FFA)	L	37	-32	-60	-16	3.13		
Occipital Fusiform Gyrus	L	18	-18	-80	-16	3.11		
Lateral Occipital Cortex, inferior division	L	19	-38	-78	-16	3.00		
Target Eyes > (Target and Eyes)								
Superior Parietal Lobule	L	40	-42	-40	56	3.39	0.000461	1727
Precentral Gyrus	L	6	-28	-22	64	3.15		
Postcentral Gyrus	L	40	-42	-30	42	2.98		
Postcentral Gyrus	L	2	-52	-26	40	2.94		
Occipital Fusiform Gyrus	R	18	30	-76	-12	3.68	0.0158	1027
Temporal Occipital Fusiform Cortex (FFA)	R	37	26	-50	-18	2.96		
Occipital Fusiform Gyrus	R	19	38	-68	-14	2.87		
Lateral Occipital Cortex, inferior division	R	18	32	-88	2	2.79		
Occipital Pole	R	17	18	-96	2	2.79		

Table 3.4. Foci of Activation from Condition Contrast Analysis in the Neurotypical Group

Regions activated more in one condition than in another, namely between the Target Eyes condition and the Target Alone condition ('Target Eyes > Target'), between the Target Eyes and the Eyes Alone condition ('Target Eyes > Eyes'), and between the Target Eyes condition and the combination of the Target Alone and Eyes Alone conditions ('Target Eyes > (Target and Eyes)'). All condition contrasts were corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels.

Region		BA	Overlap X	Y	Z	BSR OFC	BSR dlPFC	BSR vlPFC	Right Orbital Frontal Cortex x	y	z	size	lag	Correlations RT	Seed	Right Dorsolateral Prefrontal Cortex x	y	z	size	lag	Correlations RT	Seed	Left Ventrolateral Prefrontal Cortex x	y	z	size	lag	Correlations RT	Seed
Dorsal Anterior Cingulate	R	24/32	8	8	32	3.07		2.33	8	4	44	116	2	0.33	0.67								12	8	36	128	6	0.54	0.51
Rostral Anterior Cingulate	N/A	32	0	40	-4	3.86		2.06	-4	40	-4	21	4	0.57	0.84								0	36	-4	49	2	0.43	0.59
Ventral Anterior Cingulate	R	25/32	12	32	-8	3.37		3.26	12	24	-8	76	5	0.43	0.60								8	36	-8	77	1	0.58	0.67
Posterior Cingulate	R	23/31	8	-48	32	7.68		2.41	8	-48	36	71	3	0.40	0.83								8	-48	24	19	6	0.60	0.41
Posterior Cingulate	R	31	8	-44	32	4.42	1.87		8	-48	36	71	3	0.40	0.83	12	-40	32	43	3	0.35	-0.33							
Dorsomedial Prefrontal Cortex (dmPFC)	N/A	10	8	60	20		2.14	2.85								0	64	20	78	6	0.46	-0.53	8	64	24	16	2	0.52	0.37
Ventromedial Prefrontal Cortex (vmPFC)	N/A	10	-4	52	-4		1.80	2.15								0	52	-8	54	3	0.42	-0.39	-4	56	-4	15	2	0.61	0.45
Orbital Frontal Cortex (OFC)	R	11/47	28	28	-20		2.93	4.69								28	28	-20	20	1	0.48	-0.45	24	32	-20	18	1	0.40	0.52

Table 3.5. Overlapping Regions from the Neurotypical Seed-PLS Analyses

MNI coordinates and BSR values in the overlap columns represent the location and BSR of the overlapping voxel. MNI coordinates for each of the seeds represent location of max voxel in the cluster. Correlation values from the peak cluster voxel for each overlapping region with both activity in the seed and with RT were also included.

(I) Accuracy Condition 1	(J) Accuracy Condition 2	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Target	Eyes	-43.161*	5.821	.000	-61.246	-25.076
	Target Eyes	-10.667*	2.609	.008	-18.773	-2.560
	Standard	-46.013*	5.518	.000	-63.157	-28.869
Eyes	Target	43.161*	5.821	.000	25.076	61.246
	Target Eyes	32.494*	5.753	.000	14.621	50.368
	Standard	-2.852	2.178	1.000	-9.618	3.915
Target Eyes	Target	10.667*	2.609	.008	2.560	18.773
	Eyes	-32.494*	5.753	.000	-50.368	-14.621
	Standard	-35.346*	5.469	.000	-52.338	-18.354
Standard	Target	46.013*	5.518	.000	28.869	63.157
	Eyes	2.852	2.178	1.000	-3.915	9.618
	Target Eyes	35.346*	5.469	.000	18.354	52.338

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 3.6. Pairwise Comparisons of Percent Correct Responses on Social Target Detection Task in Individuals with High-Functioning Autism.

Repeated measure ANOVA revealed a significant main effect of condition on percent correct responses in the participants with high-functioning autism ($F(1.41, 18.27) = 46.14$, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method.

(I) Latency Condition 1	(J) Latency Condition 2	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Target	Eyes	138.802*	21.291	.000	72.651	204.953
	Target Eyes	13.071	7.284	.576	-9.560	35.702
	Standard	187.935*	18.884	.000	129.263	246.608
Eyes	Target	-138.802*	21.291	.000	-204.953	-72.651
	Target Eyes	-125.731*	18.891	.000	-184.427	-67.034
	Standard	49.134*	10.680	.003	15.951	82.317
Target Eyes	Target	-13.071	7.284	.576	-35.702	9.560
	Eyes	125.731*	18.891	.000	67.034	184.427
	Standard	174.864*	14.612	.000	129.465	220.264
Standard	Target	-187.935*	18.884	.000	-246.608	-129.263
	Eyes	-49.134*	10.680	.003	-82.317	-15.951
	Target Eyes	-174.864*	14.612	.000	-220.264	-129.465

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 3.7. Pairwise Comparisons of Latency to Correct Responses on Social Target Detection Task in Individuals with High-Functioning Autism.

Repeated measure ANOVA revealed a significant main effect of condition on latency to correct responses in the participants with high-functioning autism ($F(1.45, 18.82) = 66.92$, $P \leq 0.000$). Significant findings were followed up with pair-wise t-tests corrected for multiple comparisons using the bonferroni method.

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Eyes								
Temporal Occipital Fusiform Cortex (FFA)	R	37	34	-52	-20	4.69	1.80E-14	4355
Temporal Occipital Fusiform Cortex (FFA)	R	37	36	-60	-18	4.59		
Occipital Fusiform Gyrus	R	19	38	-68	-14	4.21		
Lateral Occipital Cortex, inferior division	R	19	42	-80	-6	4.11		
Lateral Occipital Cortex, inferior division	R	18	34	-82	-16	4.09		
Lateral Occipital Cortex, superior division	R	18	28	-76	22	4.05		
Occipital Fusiform Gyrus	L	19	-34	-74	-16	4.80	1.30E-10	2807
Occipital Fusiform Gyrus	L	19	-32	-70	-18	4.72		
Lateral Occipital Cortex, inferior division	L	19	-44	-80	-12	4.16		
Temporal Occipital Fusiform Cortex (FFA)	L	37	-34	-60	-24	4.09		
Temporal Occipital Fusiform Cortex (FFA)	L	37	-40	-60	-10	3.99		
Lateral Occipital Cortex, inferior division	L	19	-34	-82	6	3.98		
Target								
Postcentral Gyrus	L	40	-44	-36	48	4.43	4.50E-11	1943
Superior Parietal Lobule	L	40	-34	-44	54	4.12		
Superior Parietal Lobule	L	40	-38	-38	54	3.93		
Precentral Gyrus	L	4	-32	-24	66	3.87		
Postcentral Gyrus	L	2	-46	-34	58	3.86		
Postcentral Gyrus	L	3	-42	-24	54	3.86		
Supplementary Motor Cortex	N/A	24	0	-4	48	3.61	1.43E-05	774
Supplementary Motor Cortex	R	6	2	8	52	3.52		
Supplementary Motor Cortex	R	6	2	2	56	3.40		
Supplementary Motor Cortex	L	24	-4	-2	48	3.34		
Supplementary Motor Cortex	R	6	2	0	60	3.26		
Anterior Cingulate Gyrus, dorsal	R	32	8	24	26	3.22		
Supramarginal Gyrus, anterior division	R	40	48	-34	54	3.68	0.0125	313
Supramarginal Gyrus, posterior division	R	40	50	-38	46	3.57		
Superior Parietal Lobule	R	2	40	-40	62	3.46		
Supramarginal Gyrus, posterior division	R	40	52	-44	48	3.17		
Superior Parietal Lobule	R	5	34	-44	62	3.07		
Intraparietal Sulcus, posterior division (hIP3)	R	40	38	-42	52	3.02		

Table 3.8. Foci of Activation from Main Effects Analysis of the Eyes Alone and Target Alone Conditions in the Individuals with High-Functioning Autism

Regions showing a main effect for condition were identified through a mixed effects analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.3$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels.

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Target Eyes								
Postcentral Gyrus	L	40	-40	-30	48	4.77	1.40E-28	6415
Postcentral Gyrus	L	3	-38	-26	52	4.55		
Postcentral Gyrus	L	40	-40	-32	40	4.42		
Postcentral Gyrus	L	40	-34	-38	58	4.40		
Supplementary Motor Cortex	R	6	4	6	50	4.35		
Intraparietal Sulcus, posterior division (hIP3)	L	40	-32	-40	44	4.30		
Cerebellum	R	*	24	-52	-26	4.38	5.00E-15	2558
Cerebellum, VI	R	*	32	-52	-24	4.27		
Cerebellum, VI	R	*	32	-48	-26	4.24		
Occipital Fusiform Gyrus	R	19	36	-68	-18	4.18		
Occipital Fusiform Gyrus	R	19	32	-68	-12	4.14		
Occipital Fusiform Gyrus	R	18	26	-72	-14	4.11		
Occipital Fusiform Gyrus	L	19	-36	-72	-18	4.35	5.59E-14	2311
Lateral Occipital Cortex, inferior division	L	37	-48	-64	-10	4.24		
Inferior Temporal Gyrus, temporooccipital part	L	37	-50	-62	-14	4.18		
Temporal Fusiform Cortex, posterior division	L	37	-34	-50	-26	4.18		
Occipital Fusiform Gyrus	L	18	-28	-80	-14	4.13		
Lateral Occipital Cortex, inferior division	L	37	-44	-70	-8	4.12		
Intraparietal Sulcus, posterior division (hIP3)	R	40	36	-46	46	4.44	1.06E-10	1595
Supramarginal Gyrus, posterior division	R	40	46	-36	52	4.00		
Superior Parietal Lobule	R	7	36	-50	56	3.86		
Intraparietal Sulcus, posterior division (hIP3)	R	7	30	-58	42	3.85		
Postcentral Gyrus	R	40	44	-30	50	3.81		
Supramarginal Gyrus, posterior division	R	40	52	-42	48	3.66		
Precentral Gyrus	R	9	38	4	30	3.90	0.000119	535
Precentral Gyrus	R	6	54	0	42	3.11		
Precentral Gyrus	R	9	56	12	34	3.06		
Precentral Gyrus	R	9	54	4	34	3.01		
Dorsolateral Prefrontal Cortex	R	9	36	18	28	2.83		
Dorsolateral Prefrontal Cortex	R	*	38	18	24	2.64		
Precentral Gyrus	L	6	-54	6	32	3.68	0.000473	452
Precentral Gyrus	L	13	-36	6	22	5.00		
Dorsolateral Prefrontal Cortex	L	44	-52	8	12	5.00		
Dorsolateral Prefrontal Cortex	L	9	-42	10	26	5.00		
Precentral Gyrus	L	6	-52	2	36	5.00		
Central Opercular Cortex	L	13	-42	-2	12	5.00		
Putamen, lentiform nucleus	L	*	-22	4	-4	3.51	0.00556	316
Putamen	L	*	-18	12	-12	3.33		
Putamen	L	*	-20	14	-2	3.08		
Orbital Frontal Cortex	L	47	-28	26	-6	4.01	0.00567	315
Insular Cortex	L	*	-28	20	6	3.38		
Insular Cortex	L	13	-36	12	0	3.35		
Frontal Operculum Cortex	L	13	-34	20	6	3.14		
Insular Cortex	R	47	36	22	-2	3.77	0.00759	300
Central Opercular Cortex	R	13	46	6	0	3.26		
Central Opercular Cortex	R	13	42	2	8	3.00		
Frontal Operculum Cortex	R	13	34	16	10	2.80		
Orbital Frontal Cortex	R	47	42	22	-10	2.78		
Dorsolateral Prefrontal Cortex	R	9	38	32	34	3.57	0.00789	298
Dorsolateral Prefrontal Cortex	R	10	38	38	20	3.13		
Dorsolateral Prefrontal Cortex	R	46	46	24	30	3.08		
Dorsolateral Prefrontal Cortex	R	46	42	48	22	3.03		
Dorsolateral Prefrontal Cortex	R	10	36	46	30	2.86		
Dorsolateral Prefrontal Cortex	R	10	40	50	14	2.72		

Table 3.9. Foci of Activation from Main Effects Analysis of the Target Eyes Condition in the Individuals with High-Functioning Autism

Regions showing a main effect for condition were identified through a mixed effects analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.3$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels.

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Target Eyes > Eyes								
Superior Parietal Lobule	L	5	-28	-46	62	3.27	0.000247	1681
Precentral Gyrus	L	3	-42	-20	60	3.23		
Postcentral Gyrus	L	2	-40	-26	46	3.16		
Postcentral Gyrus	L	3	-36	-34	52	3.09		
Precentral Gyrus	L	4	-42	-16	50	3.08		
Precentral Gyrus	L	4	-32	-20	60	3.05		
Target Eyes > (Target and Eyes)								
Postcentral Gyrus	L	3	-38	-28	52	3.01	0.00175	1175
Precentral Gyrus	L	4	-32	-20	60	2.96		
Intraparietal Sulcus, posterior division (hIP3)	L	40	-36	-44	48	2.91		
Postcentral Gyrus	L	40	-40	-26	46	2.89		
Precentral Gyrus	L	4	-30	-24	64	2.86		
Precentral Gyrus	L	4	-38	-20	58	2.86		

Table 3.10. Foci of Activation from Condition Contrast Analysis in the High-Functioning Autism Group

Regions activated more in one condition than in another, namely between the Target Eyes and the Eyes Alone condition ('Target Eyes > Eyes'), and between the Target Eyes condition and the combination of the Target and Eyes conditions ('Target Eyes > (Target and Eyes)'). No regions survived the analysis of the Target Eyes and the Target Alone Condition ('Target Eyes > Target Alone') The Target Eyes > Eyes analysis was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The Pure Social Target condition was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels.

Regions Where Individuals with Autism Activate to a Greater Extent than Typically Developing Controls

Main Cluster Local Maxima		BA	X	Y	Z	Max Z	Corrected p-value	Size
Eyes								
Temporal Occipital Fusiform Cortex (FFA)	R	37	36	-48	-14	3.09	0.00127	1874
Precuneus	R	29	2	-56	10	2.94		
Cerebellum, VI	R	*	36	-60	-26	2.93		
Lingual Gyrus	R	19	8	-56	-8	2.92		
Temporal Occipital Fusiform Cortex (FFA)	R	37	28	-50	-12	2.90		
Parahippocampal Gyrus, posterior division	R	*	32	-34	-12	2.89		
Dorsomedial Prefrontal Cortex	R	9	24	44	38	3.32	0.00705	1445
Dorsomedial Prefrontal Cortex	R	9	14	52	36	3.07		
Dorsomedial Prefrontal Cortex	R	9	26	34	28	2.98		
Dorsomedial Prefrontal Cortex	R	9	22	36	42	2.93		
Dorsomedial Prefrontal Cortex	N/A	10	0	68	16	2.91		
Dorsomedial Prefrontal Cortex	R	10	12	66	20	2.86		
Caudate	R	*	20	2	24	2.96	0.0231	1169
Caudate	R	*	10	18	2	2.80		
Precentral Gyrus	R	*	38	6	22	2.77		
Caudate	R	*	14	20	6	2.65		
Main Cluster		**BA**	**X**	**Y**	**Z**	**Max Z**	**Uncorrected p-value**	**Size**
Target Eyes > Target								
Angular Gyrus	L	40	-46	-52	44	2.85	0.0044	19
Target Eyes > (Target and Eyes)								
Superior Frontal Gyrus	L	8	-4	18	56	2.53	0.0114	86
Supramarginal Gyrus, posterior division	L	40	-50	-44	42	2.34	0.0193	12
Angular Gyrus (Pga)	R	40	54	-54	20	2.31	0.0209	222

Table 3.11. Foci of Activation Identifying Regions in which Individuals with Autism Exhibit Increased Activation as Compared to Neurotypical Controls

Regions activated more by individuals with autism as compared to neurotypical controls. The Eyes Alone analysis was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The Target Eyes > Target contrast represents an uncorrected analysis in which regions were considered significant if they were comprised of 15 contiguous voxels and reached a Z-statistic threshold of $Z > 2.3$, which is roughly equivalent to an uncorrected $p < 0.02$. Finally, the Pure Social Target condition was analyzed at an uncorrected Z-statistic threshold of $Z > 1.961$ ($p = 0.05$).

Regions Where Typically Developing Participants Activate to a Greater Extent than Individuals with Autism								
Main Cluster **Local Maxima**		**BA**	**X**	**Y**	**Z**	**Max Z**	**Corrected p-value**	**Size**
Target								
Lateral Occipital Cortex, superior division	R	19	38	-72	42	3.50	0.0289	776
Lateral Occipital Cortex, superior division	R	7	38	-68	48	3.39		
Lateral Occipital Cortex, superior division	R	7	34	-66	50	3.37		
Lateral Occipital Cortex, superior division	R	19	30	-64	40	3.06		
Lateral Occipital Cortex, superior division	R	40	44	-58	52	3.06		
Lateral Occipital Cortex, superior division	R	39	38	-72	34	2.94		
Main Cluster		**BA**	**X**	**Y**	**Z**	**Max Z**	**Uncorrected p-value**	**Size**
Target Eyes > Eyes								
Putamen	R	*	22	12	-2	2.87	0.0041	135
Putamen	R	*	30	-16	2	2.79	0.0053	156
Precuneus	R	7	10	-72	46	2.76	0.0058	110
Dorsomedial Prefrontal Cortex	R	8	10	46	44	2.71	0.0067	115
Superior Temporal Gyrus, posterior division	R	41	46	-36	6	2.70	0.0069	210
Middle Temporal Gyrus, posterior division	R	22	50	-18	-12	2.62	0.0088	219
Target Eyes > (Target and Eyes)								
Superior Parietal Lobule	L	5	-40	-44	62	2.54	0.0111	32
Middle Temporal Gyrus, posterior division	R	22	46	-22	-12	2.53	0.0114	212
Temporal Occipital Fusiform Cortex (FFA)	L	37	-32	-60	-12	2.53	0.0114	55
Middle Temporal Gyrus, posterior division	R	22	46	-36	0	2.51	0.0121	209
Precentral Gyrus	R	6	56	0	22	2.51	0.0121	223
Lateral Occipital Cortex, superior division	L	19	-36	-88	14	2.47	0.0135	40
Lateral Occipital Cortex, superior division	L	*	-32	-74	16	2.45	0.0143	53
Lateral Occipital Cortex, inferior division	L	19	-48	-72	4	2.33	0.0198	15
Superior Temporal Gyrus, posterior division	L	*	-64	-32	0	2.33	0.0198	0
Insular Cortex	L	*	-36	-12	4	2.27	0.0232	43

Table 3.12. Foci of Activation Identifying Regions in which Neurotypical Participants Exhibit Increased Activation as Compared to Individuals with High-Functioning Autism

Regions activated more by neurotypical participants as compared to individuals with high-functioning autism. The Target Alone analysis was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The Target Eyes > Eyes contrast represents an uncorrected analysis in which regions were considered significant if they were comprised of 15 contiguous voxels and reached a Z-statistic threshold of $Z > 2.3$, which is roughly equivalent to an uncorrected $p < 0.02$. The Pure Social Target condition was analyzed at an uncorrected Z-statistic threshold of $Z > 1.961$ ($p = 0.05$).

Region		BA	Overlap X	Y	Z	BSR OFC	BSR dlPFC	Right Orbital Frontal Cortex x	y	z	size	lag	Correlations RT	Seed	Right Dorsolateral Prefrontal Cortex x	y	z	size	lag	Correlations RT	Seed
Amygdala/Hippocampus	L	*	-12	-12	-16	-6.58	-4.05	-12	-12	-16	133	2	-0.60	0.79	-12	-12	-16	49	6	-0.70	-0.34
Cingulate Cortex Anterior, dorsal	L	24	-4	4	40	1.89	2.01	-8	4	36	407	3	0.67	-0.84	0	4	44	36	3	0.79	0.78
Cingulate Cortex Anterior, ventral	R	25	0	20	-8	-9.22	-2.22	0	20	-8	11222	4	-0.68	0.47	4	20	0	22	5	-0.52	-0.30
Cingulate Cortex Posterior	R	29	12	-44	8	-3.42	-2.69	12	-44	8	16	1	-0.76	0.54	4	-48	4	2507	4	-0.74	-0.57
Hippocampus	L	*	-28	-24	-16	-4.67	-2.52	-28	-24	-16	66	1	-0.47	0.44	-24	-16	-20	28	7	-0.38	-0.78

Table 3.13. Overlapping Regions from the Between Group Seed-PLS Analyses

MNI coordinates and BSR values in the overlap columns represent the location and BSR of the overlapping voxel. MNI coordinates for each of the seeds represent location of max voxel in the cluster. Correlation values from the peak cluster voxel for each overlapping region with both activity in the seed and with RT were also included.

3.9. Figures

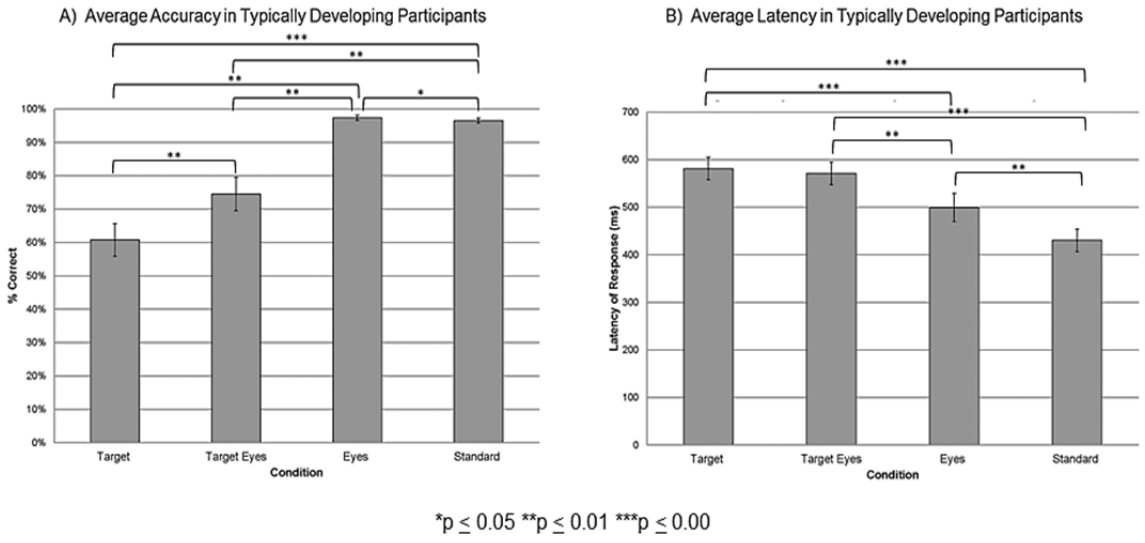

Figure 3.1. Average Accuracy and Latency to Correct Responses in Neurotypical Participants.

Graph values are means for N = 13 neurotypical participants, error bars represent SEM. All pair-wise tests were corrected for multiple comparisons using the bonferroni method. A) Average accuracy (% correct responses) in neurotypical participants on the Social Target Detection Task. B) Average latency to correct responses in neurotypical participants on the Social Target Detection Task.

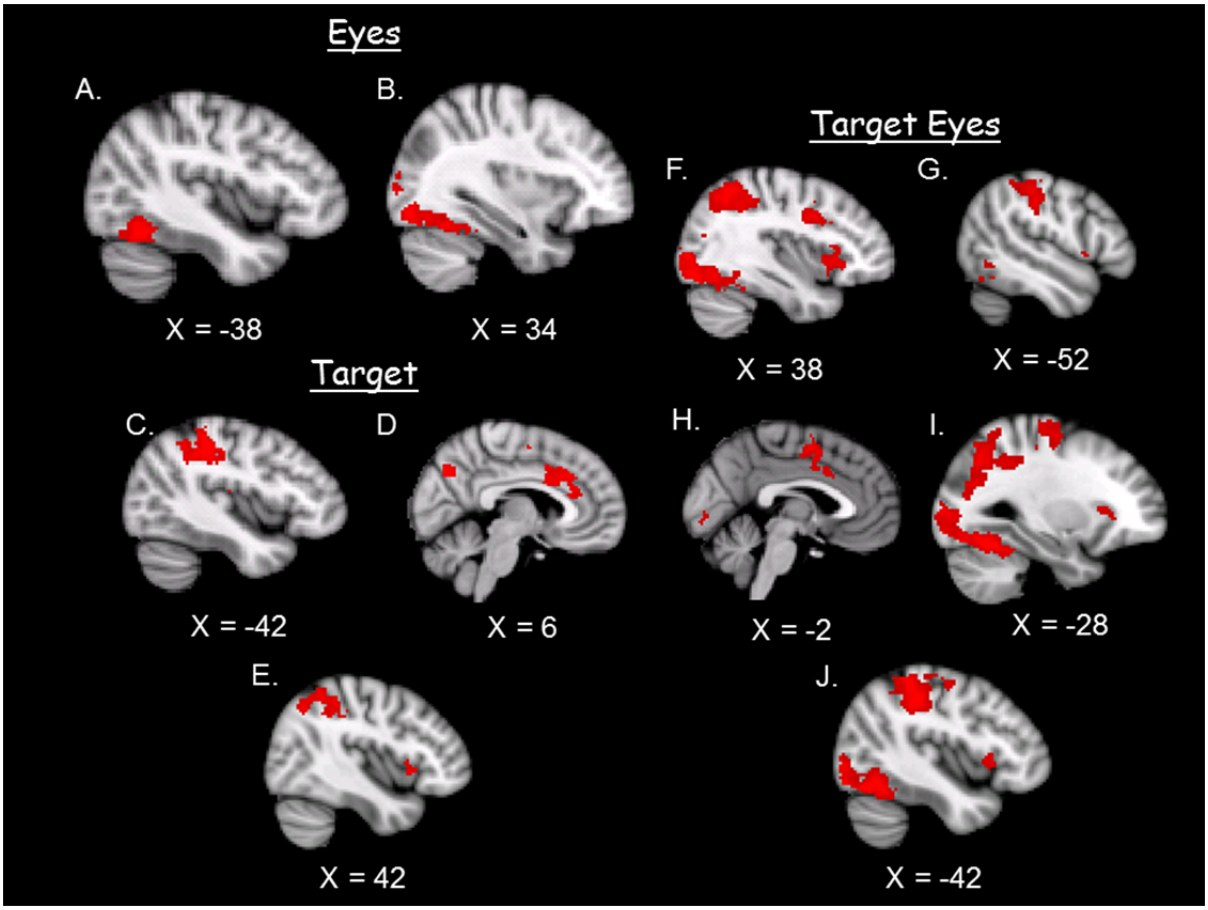

Figure 3.2. Main Effects Activation Map for the Neurotypical Group

Activation maps of the main effects were created by calculating an average map based on second level analyses using a mixed effects higher level analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.3$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The Eyes Alone condition elicited activation in the left FFA (A) and right occipital FFC, including the FFA (B). Left superior parietal cortex (C), dACC (D), and right lateral occipital cortex, including the IPS (E) activation was seen in response to the Target Alone condition. Right lateralized responses to the Target Eyes condition were found in the occipital FFC, IPS, dlPFC, and insula/OFC (F). In the left hemisphere, the Target Eyes condition engaged the Supplementary motor area (G-H), FFA, and frontal operculum cortex extending into the insula and vlPFC (I-J).

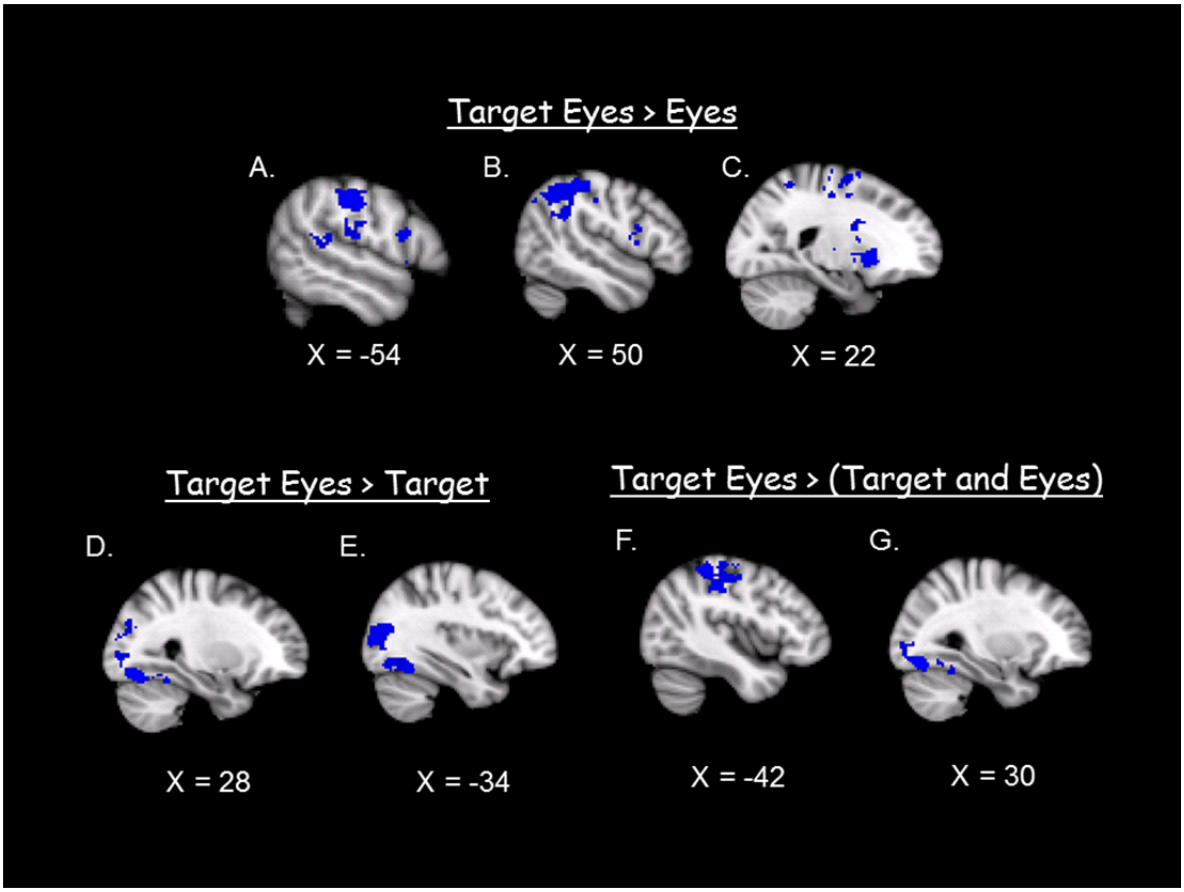

Figure 3.3. Condition Contrast Map for the Neurotypical Group

Activation maps of the condition contrasts were created by calculating an average map based on second level analyses using a mixed effects higher level analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The comparison between the Target Eyes condition and the Eyes Alone ('Target Eyes . Eyes') condition demonstrated increased activity to the Target Eyes in the left postcentral gyrus/superior parietal cortex (A), right SMG, including the angular gyrus and IPS (B), and the right lentiform nucleus of the putamen extending into the insula (C). The contrast of the Target Eyes with the Target Alone condition ('Target Eyes > Target Alone') revealed that when the target was paired with eyes there was greater recruitment in the right occipital FFC (D) and the left lateral occipital cortex (E), including the bilateral FFA. Finally, the analysis of the Pure Social Target ('Target Eyes > Target and Eyes') revealed that the left superior parietal cortex (F) and right occipital FFC, including FFA (G) were activated to a greater extent when the target was paired with the eyes than when either the target or the eyes were presented alone

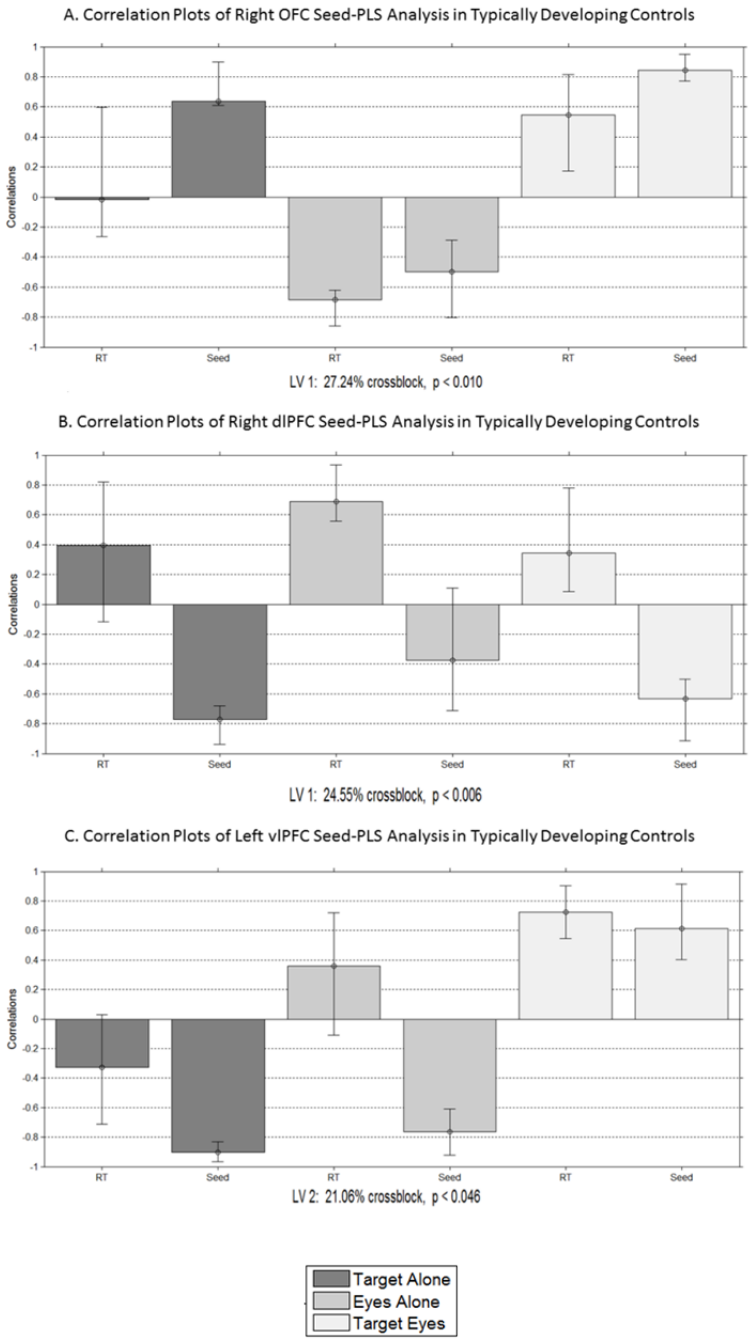

Figure 3.4. Correlation Scores from Seed-PLS Analyses in Neurotypical Participants

Graph values are correlation scores for N = 13 neurotypical participants. Seed-PLS was used to identify functional neural networks associated with activity in the right OFC (A), right dlPFC (B), and left vlPFC (C). Error bars represent 95% confidence intervals as determined via permutation testing.

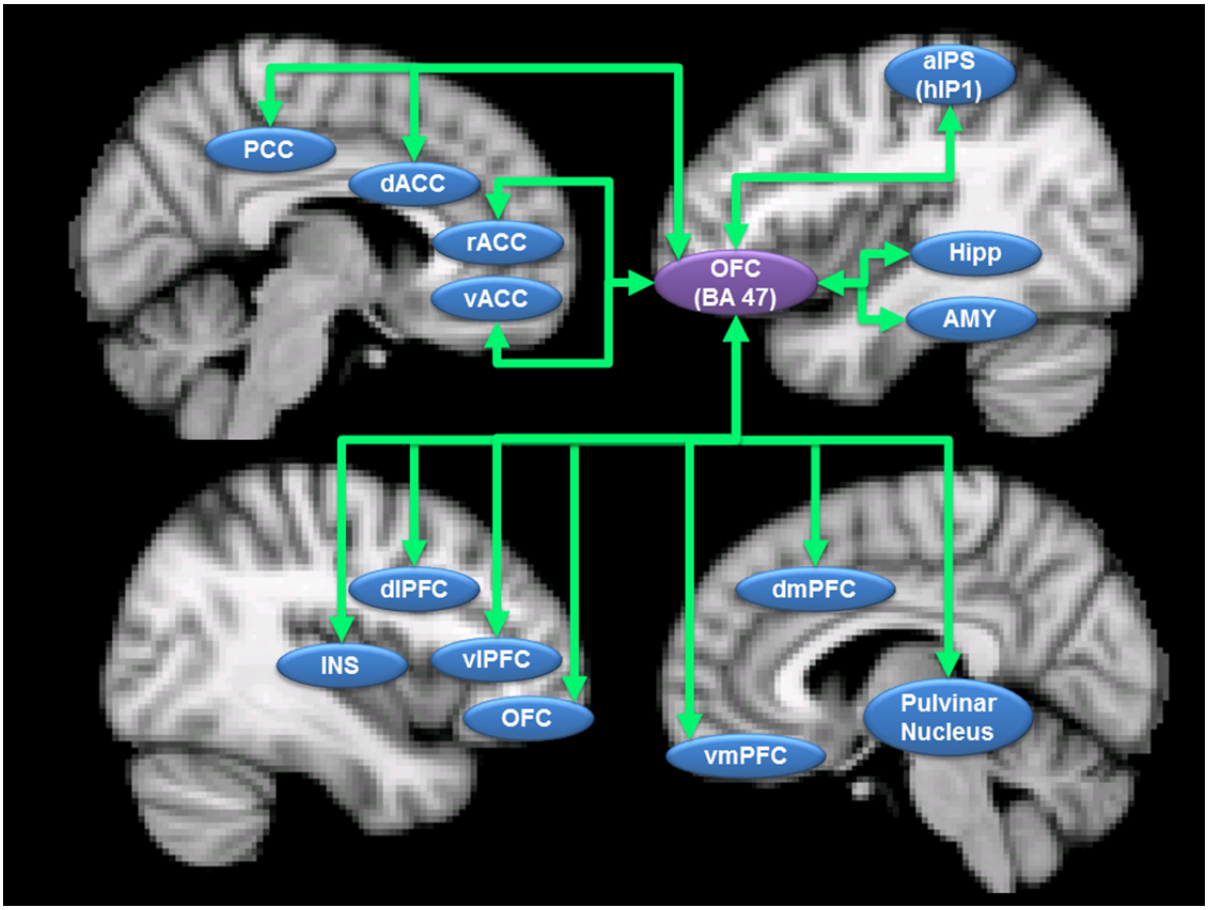

Figure 3.5. Positive Salience Network from Right OFC Seed-PLS Analysis in Neurotypical Participants

Functional connections in the positive salience neural network coupled to the right OFC in neurotypical participants. Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region.

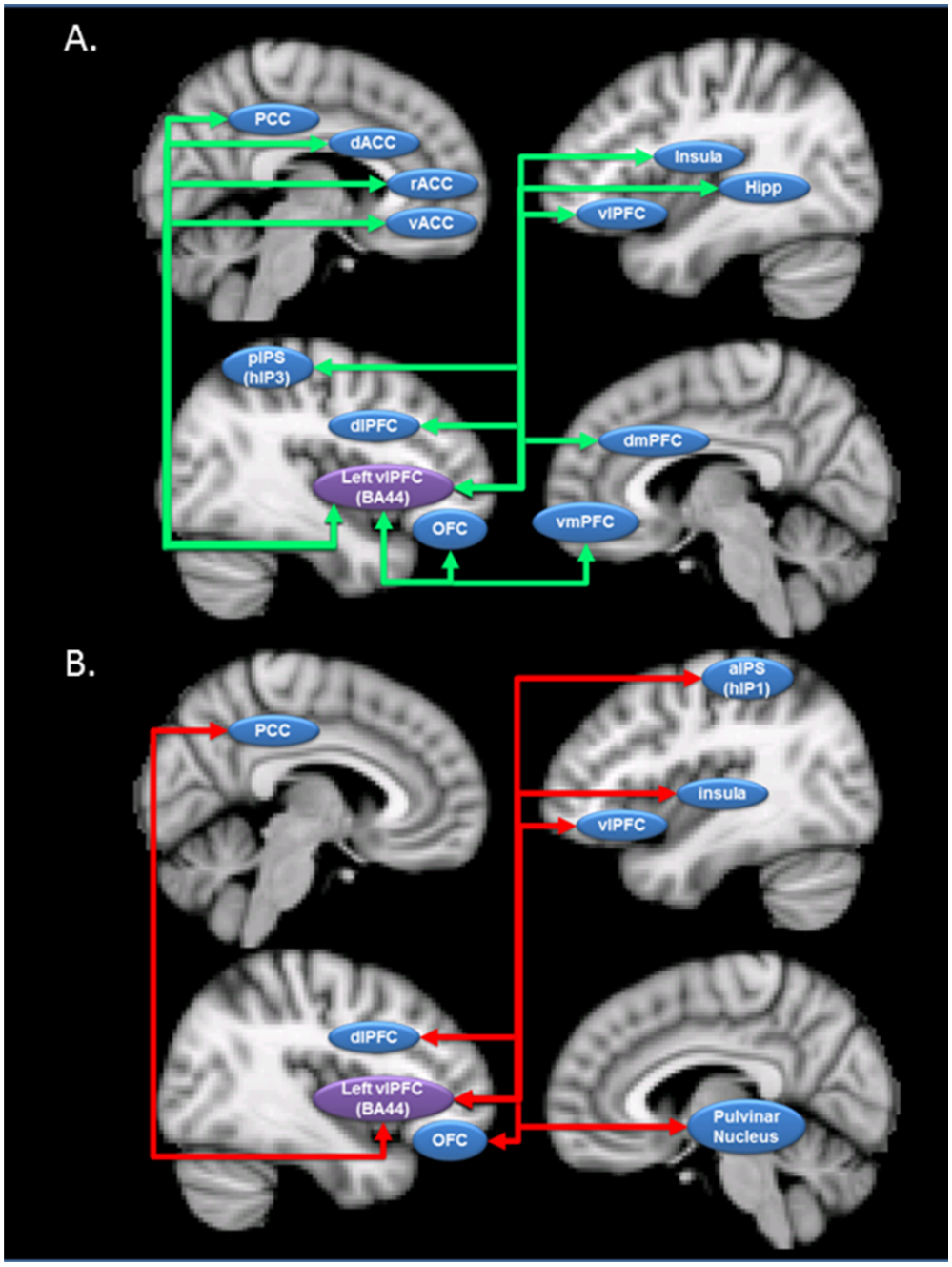

Figure 3.6. Positive and Negative Salience Networks from Left vlPFC Seed-PLS Analysis in Neurotypical Participants

Functional connections in the positive salience (A) and negative salience (B) neural networks coupled to the left vlPFC in neurotypical participants. Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region. Red arrows depict reciprocal correlations whereby increased activity in one region was associated with decreased activity in the paired region.

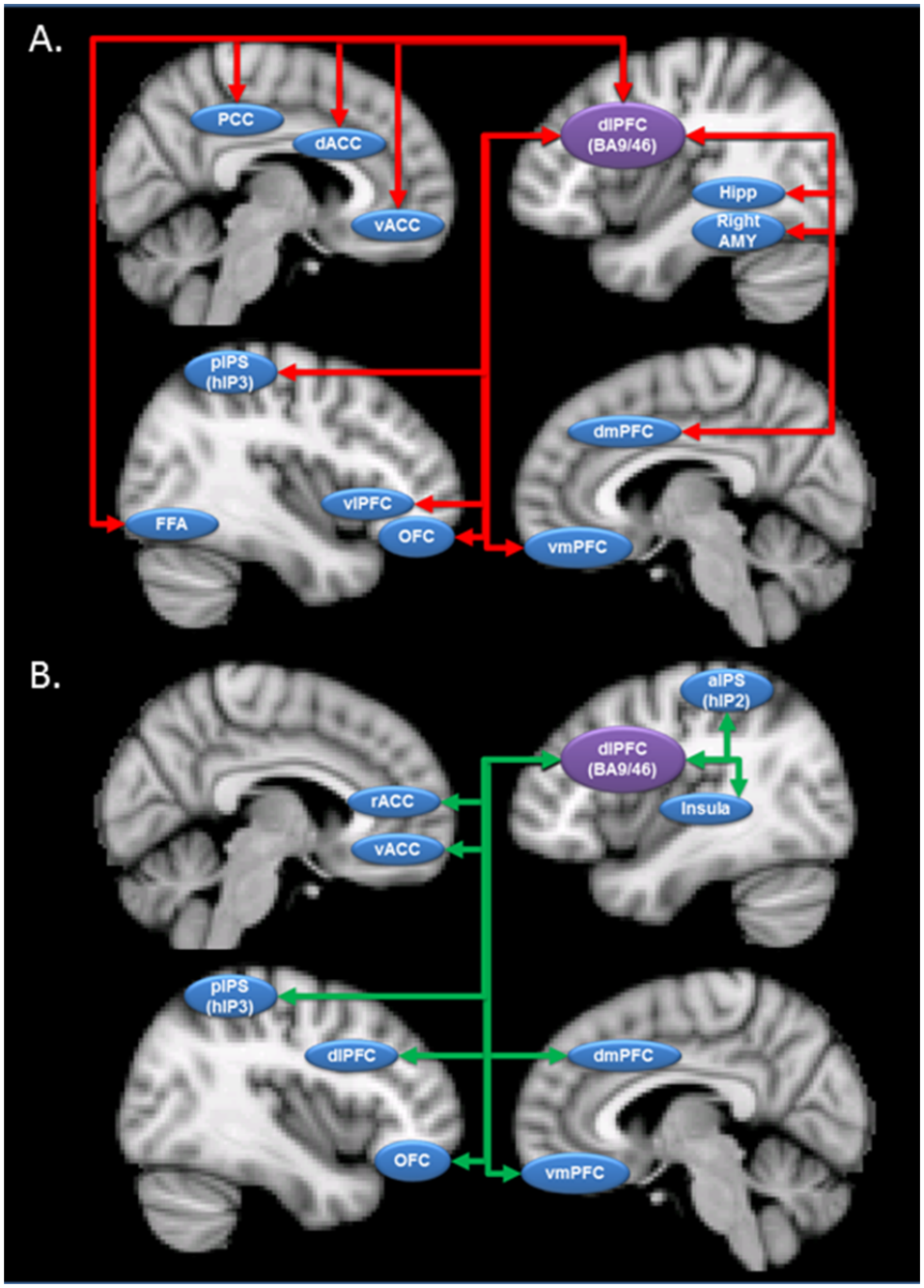

Figure 3.7. Positive and Negative Salience Networks from Right dlPFC Seed-PLS Analysis in Neurotypical Participants

Functional connections in the positive salience (A) and negative salience (B) neural network coupled to the right dlPFC in neurotypical participants. Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region. Red arrows depict reciprocal correlations whereby increased activity in one region was associated with decreased activity in the paired region.

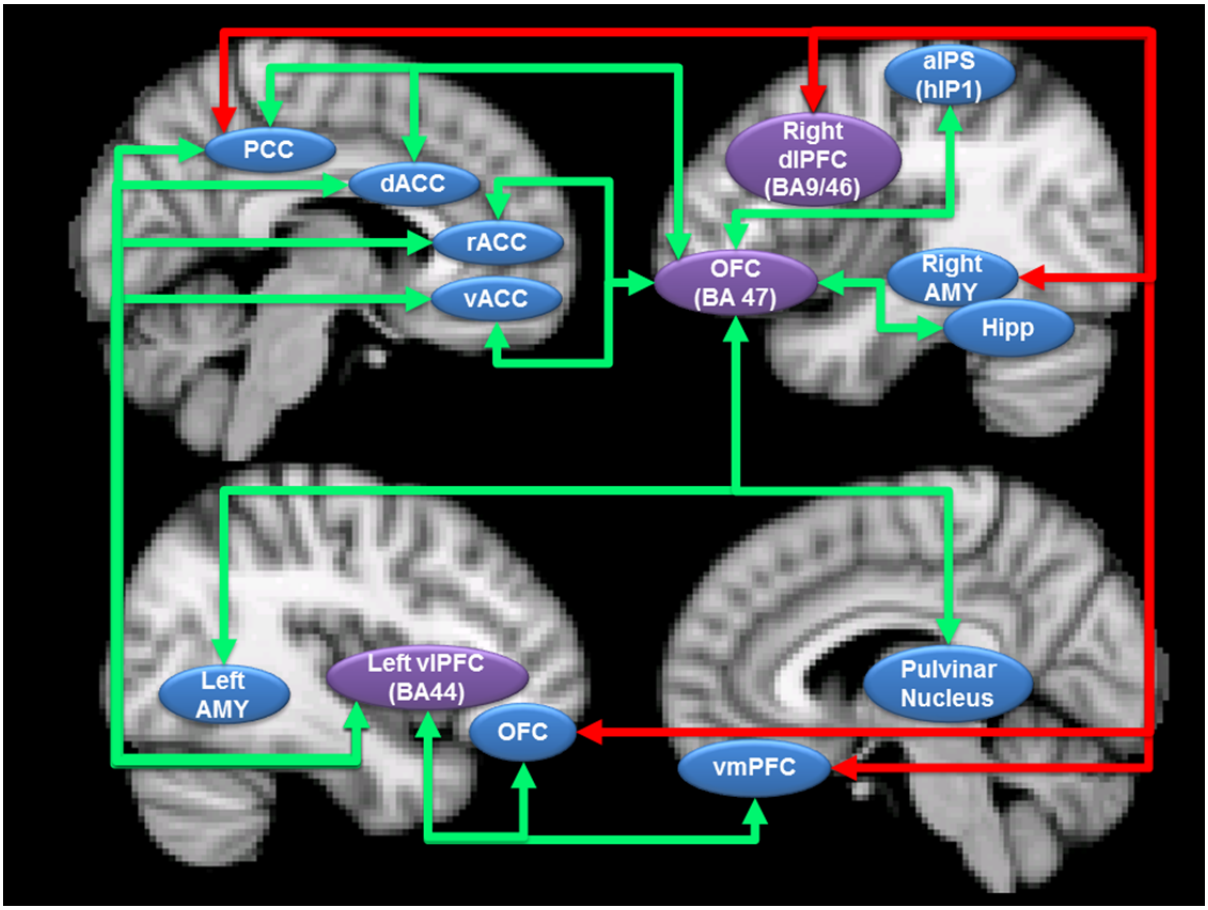

Figure 3.8. Common Functional Neural Network Associated with activity in the Right OFC, Right dlPFC, and Left vlPFC in Neurotypical Controls.

Differential activation of the right dlPFC as compared to the left vlPFC and right OFC were significantly associated with performance to the Target Eyes condition. Better performance on the Target Eyes Condition, as measured by faster RTs, was associated with increased activity in the right dlPFC and this increased dlPFC activity was negatively correlated to activity in the rest of the network, including the vlPFC and OFC seeds. Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region. Red arrows depict reciprocal correlations whereby increased activity in one region was associated with decreased activity in the paired region.

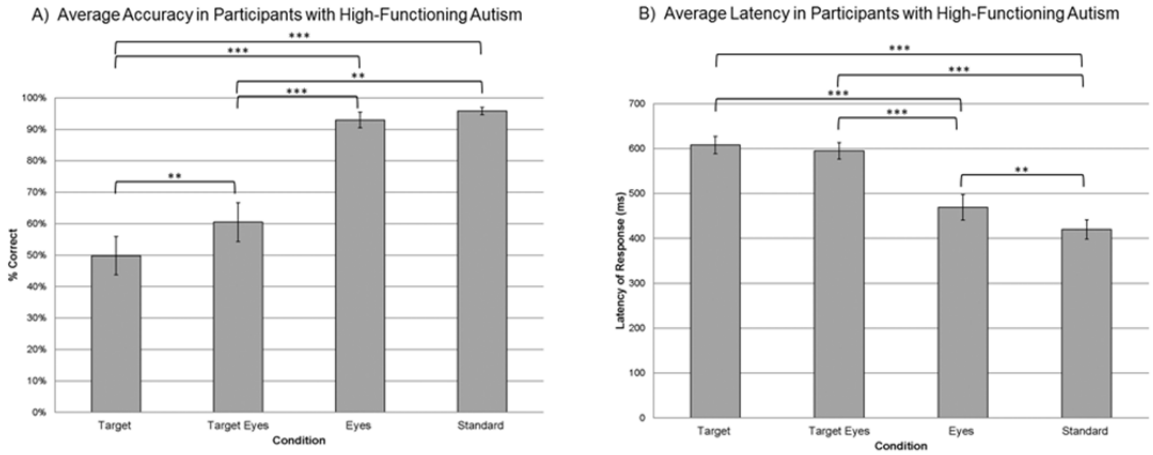

Figure 3.9. Average Accuracy and Latency to Correct Responses in Participants with High-Functioning Autism

Graph values are means for N = 14 participants with high-functioning autism, error bars represent SEM. All pair-wise tests were corrected for multiple comparisons using the bonferroni method. A) Average accuracy (% correct responses) in participants with high-functioning autism on the Social Target Detection Task. B) Average latency to correct responses in participants with high-functioning autism on the Social Target Detection Task.

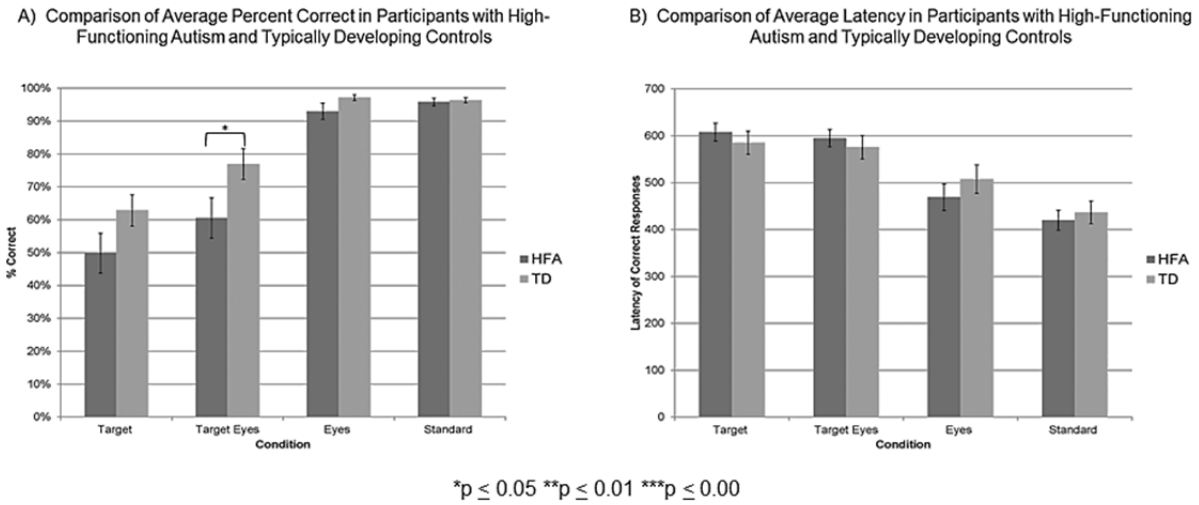

Figure 3.10. Group Comparison of Average Accuracy and Latency to Correct Responses

Graph values are means for N=14 participants per group, error bars represent SEM. A) Average accuracy (% correct responses) in participants with high-functioning autism and neurotypical controls on the Social Target Detection Task. B) Average latency to correct responses in participants with high-functioning autism and neurotypical controls on the Social Target Detection Task.

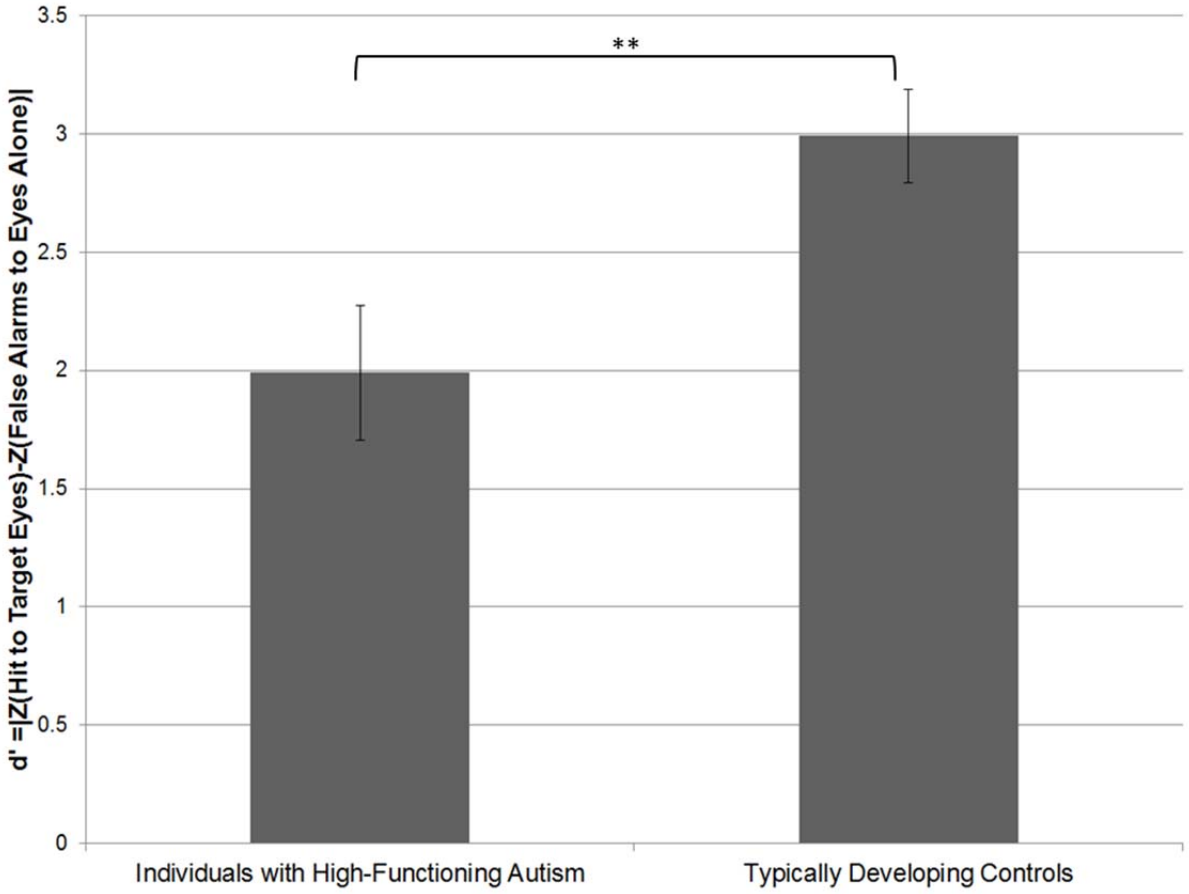

Figure 3.11. Group Comparison of Discriminability (d') Scores

Graph values are mean d' score for N=14 participants per group, error bars represent SEM. The d' was used to a measure how well individuals are able to filter the "noise" introduced into the target processing system by the task-irrelevant eye stimuli.

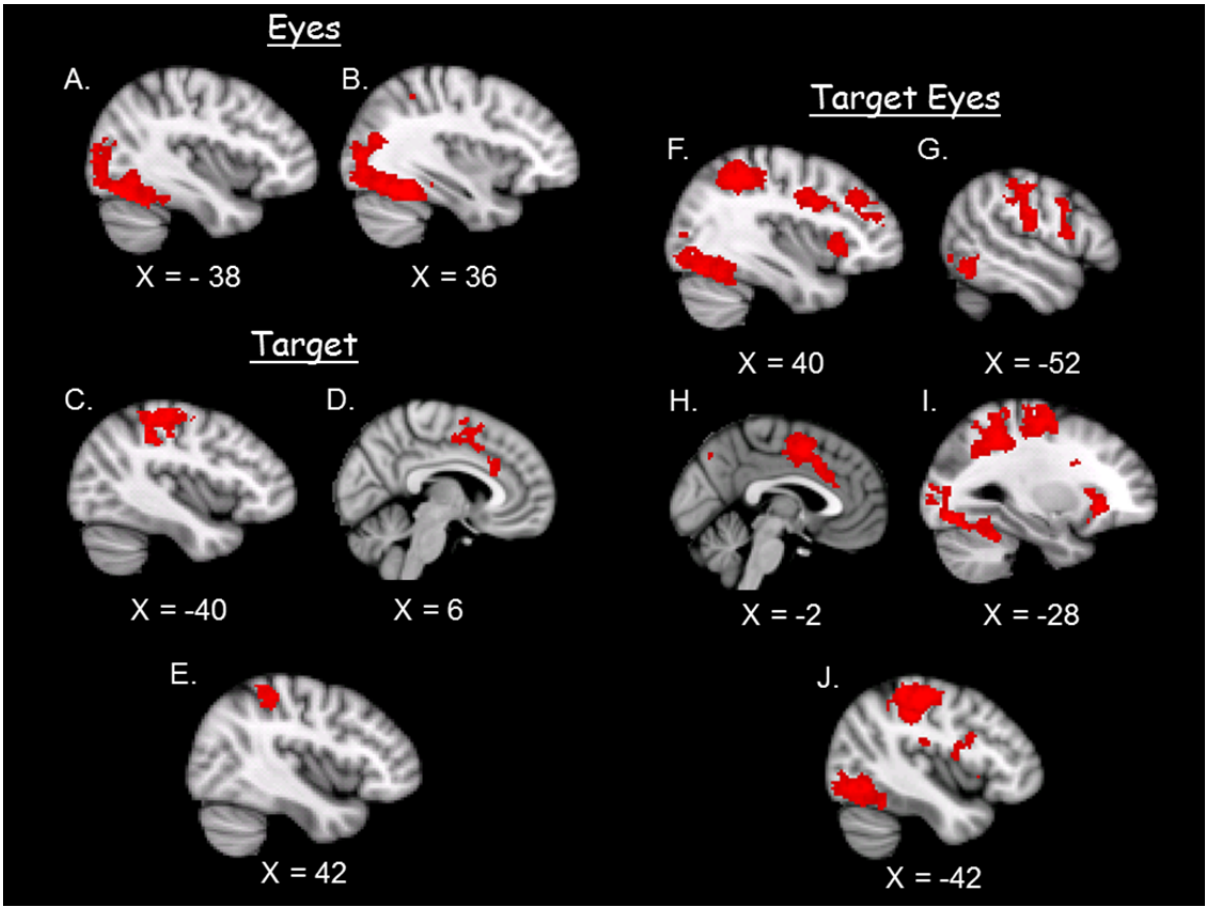

Figure 3.12. Main Effects Activation Map for Participants with High-Functioning Autism

Activation maps of the main effects were created by calculating an average map based on second level analyses using a mixed effects higher level analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 2.3$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The Eyes Alone condition elicited bilateral FFA activation (A-B). Left postcentral gyrus extending in to the superior parietal cortex (C), bilateral supplementary motor cortex and dACC (D), as well as right superior parietal cortex, including the supramarginal gyrus and the IPS (E), were activated in response to the Target Alone Condition. When the Target was paired with the eyes, there was activation in the right precentral gyrus, insula/OFC, dlPFC, and superior parietal cortex, including the IPS (F). Additionally, there was activation in the left precentral gyrus, dlPFC, postcentral gyrus extending into the IPS, occipital FFC, putamen, as well as the OFC extending into the insula in the left hemisphere (G-J).

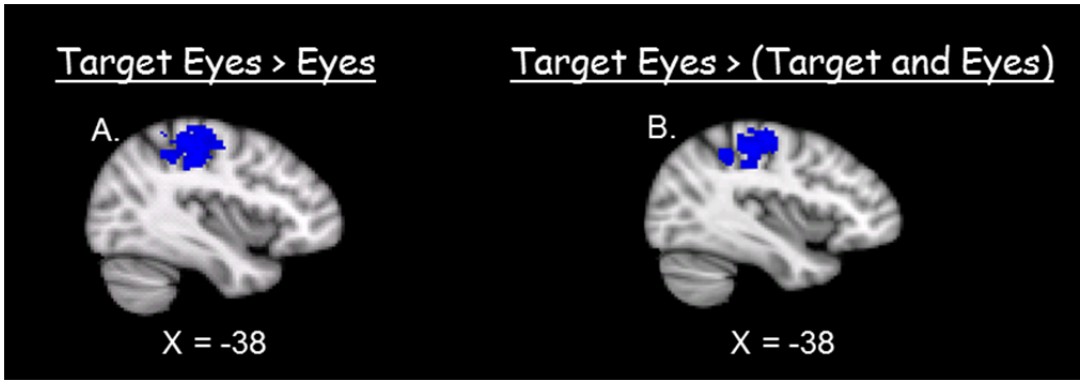

Figure 3.13. Condition Contrast Map for Participants with High-Functioning Autism

Activation maps of the contrast between the Target Eyes and the Eyes Alone condition ('Target Eyes > Eyes Alone') was created by calculating an average map based on second level analyses using a mixed effects higher level analysis and were corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$ and a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. The activation depicting where the Target Eyes were more active than both the Target Alone and the Eyes Alone condition (Pure Social Target condition; 'Target Eyes > Target and Eyes') was created in the same manner, except that it represents an uncorrected Z-statistic threshold of $Z > 1.961$. The contrast between the Target Eyes and the Eyes Alone condition revealed a single significant cluster in the superior parietal cortex, extending in to the pre- and post-central gyri (A). The analysis on the Pure Social Target condition revealed that the left postcentral gyrus, extending into the precentral gyrus and posterior IPS (B) was more active in the Target Eyes condition than either the Target or Eyes Alone conditions.

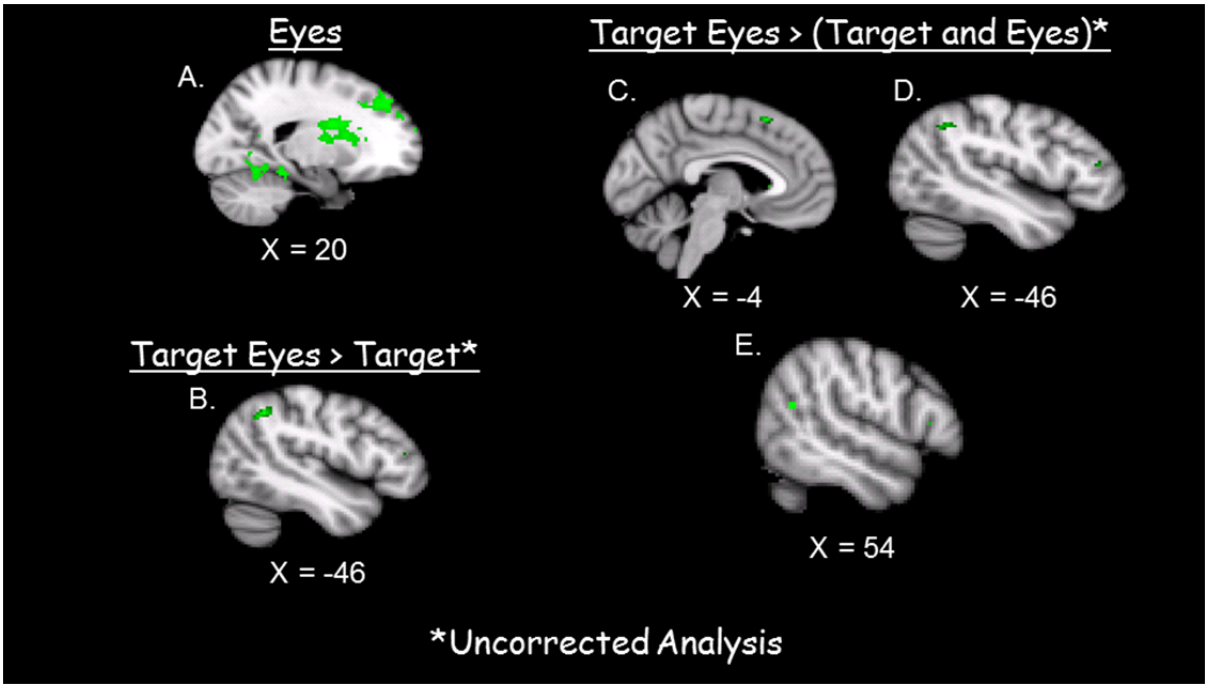

Figure 3.14. Regions where Individuals with Autism Activate more than Neurotypical Controls

Activation maps depicting regions activated more by individuals with autism as compared to neurotypical controls. The Eyes Alone analysis was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. This analysis revealed greater activation in right lateralized dmPFC, caudate, and, FFA extending rostrally into the parahippocampal gyrus (A). The Target Eyes > Target contrast represents an uncorrected analysis in which regions were considered significant if they reached a Z-statistic threshold of $Z > 2.3$, which is roughly equivalent to an uncorrected $p < 0.02$. This revealed increased activation in the left angular gyrus in the Target Eyes > Target contrast (B). Finally, the Pure Social Target condition ('Target Eyes > Target and Eyes') was analyzed at an uncorrected Z-statistic threshold of $Z > 1.961$ ($p = 0.05$) and revealed increased activation in the left SFG (C), left SMG (D), and right angular gyrus (E).

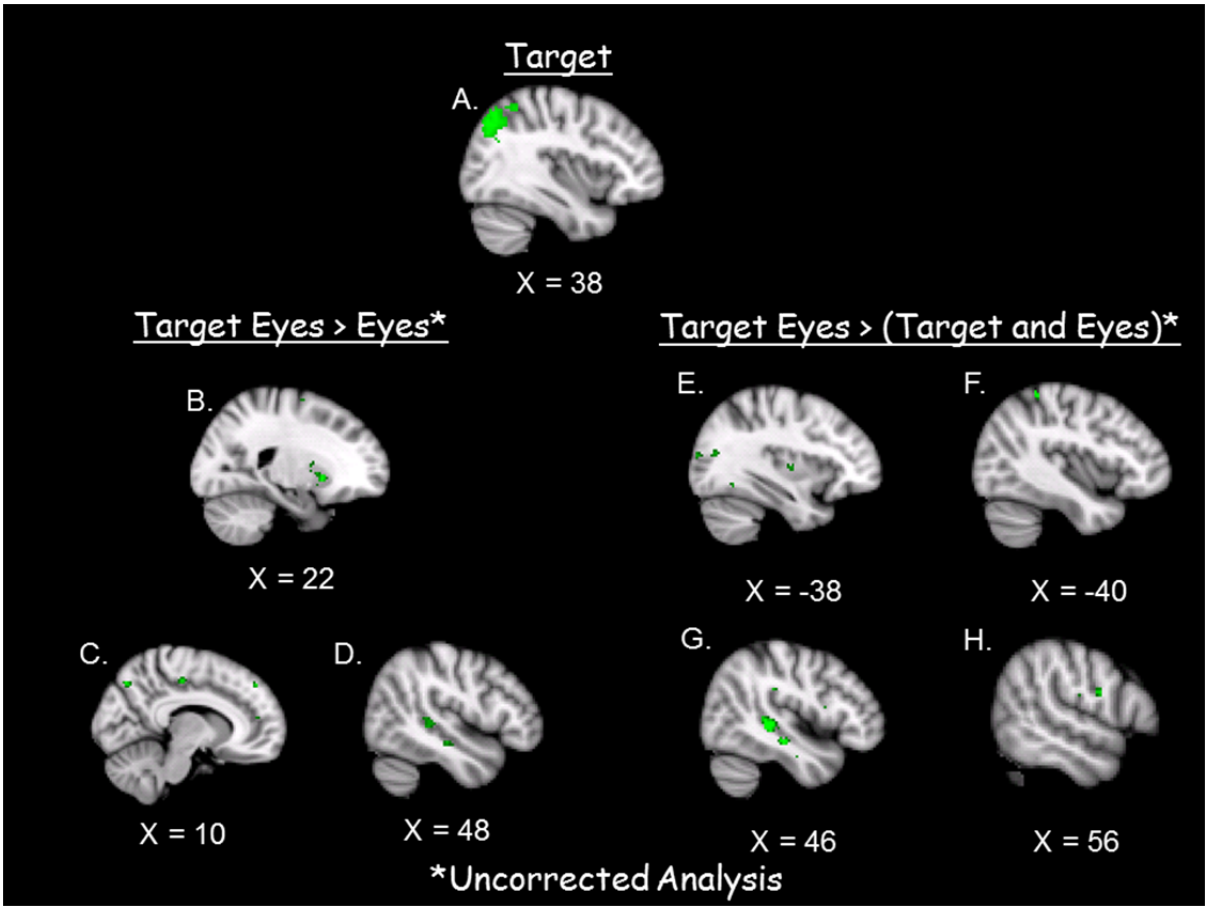

Figure 3.15. Regions where Neurotypical Participants Activate more than Individuals with Autism

Activation maps depicting regions activated more by neurotypical participants as compared to individuals with autism. The Target Alone analysis was corrected for multiple comparisons using a Z-statistic threshold of $Z > 1.961$, while maintaining a cluster-corrected threshold of $p < 0.05$ to identify contiguous voxels. This analysis revealed greater activation in the right superior division of the lateral occipital cortex (A). The Target Eyes > Eyes contrast represents an uncorrected analysis in which regions were considered significant if they reached a Z-statistic threshold of $Z > 2.3$, which is roughly equivalent to an uncorrected $p < 0.02$. In the Target Eyes > Eyes contrast revealed activation of the putamen (B), the precuneus and dmPFC (C), as well as the STG and MTG (D), in the right hemisphere. The Pure Social Target condition was analyzed at an uncorrected Z-statistic threshold of $Z > 1.961$ ($p = 0.05$) and revealed increased activation in the left FFA and insular cortex (E), left superior parietal cortex (F), as well as the right MTG (G) and precentral gyrus (H).

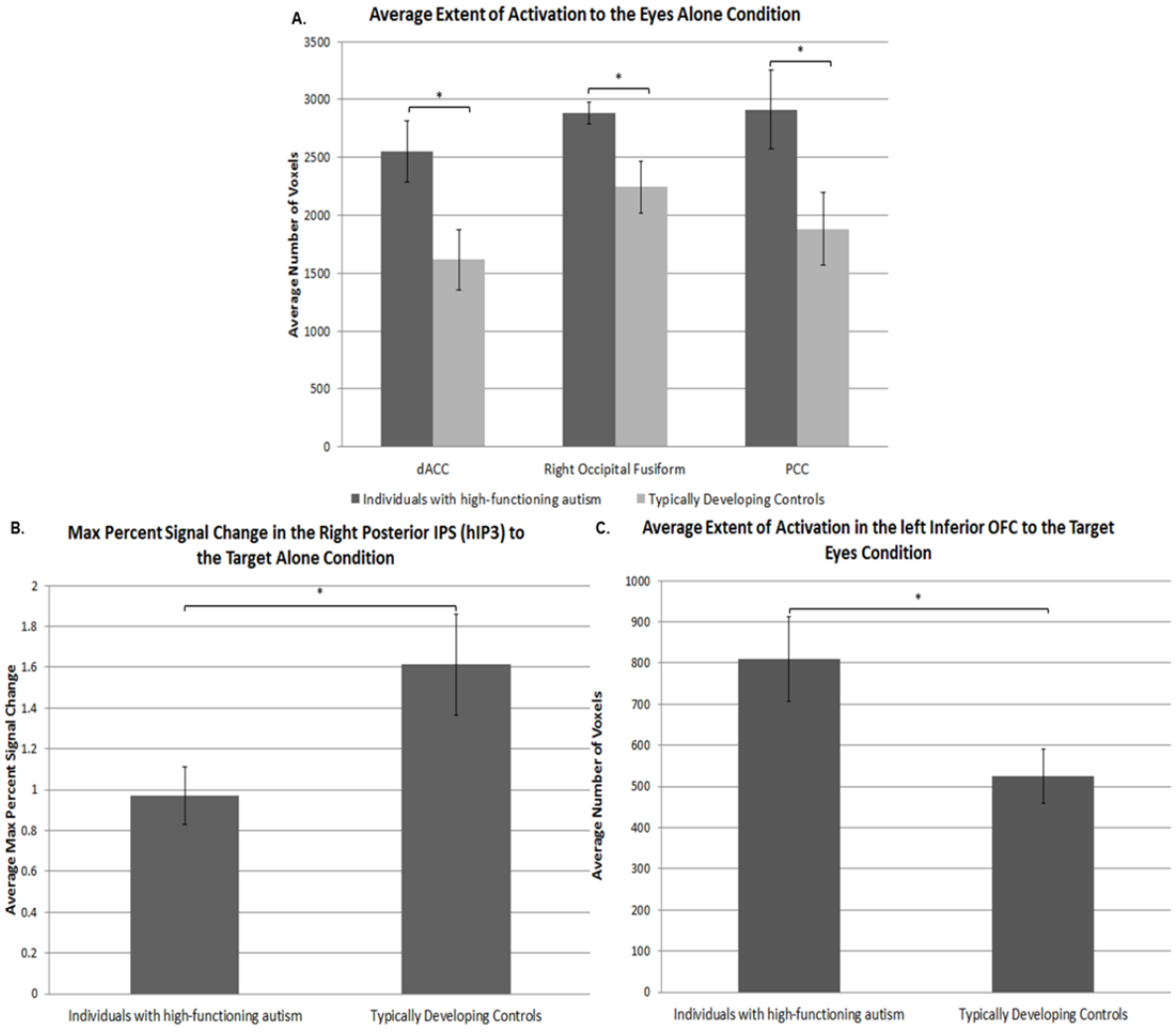

Figure 3.16. Regional Differences by Condition as Measured via ROI Analysis

Graph values are mean size of cluster activation for dACC, right occipital FFC, and PCC ROIs in the Eyes Alone condition (A) and the left inferior OFC ROI to the Target Eyes condition (C), as well as mean percent signal change in the right posterior IPS in the Target Alone condition (B). Error bars represent SEM.

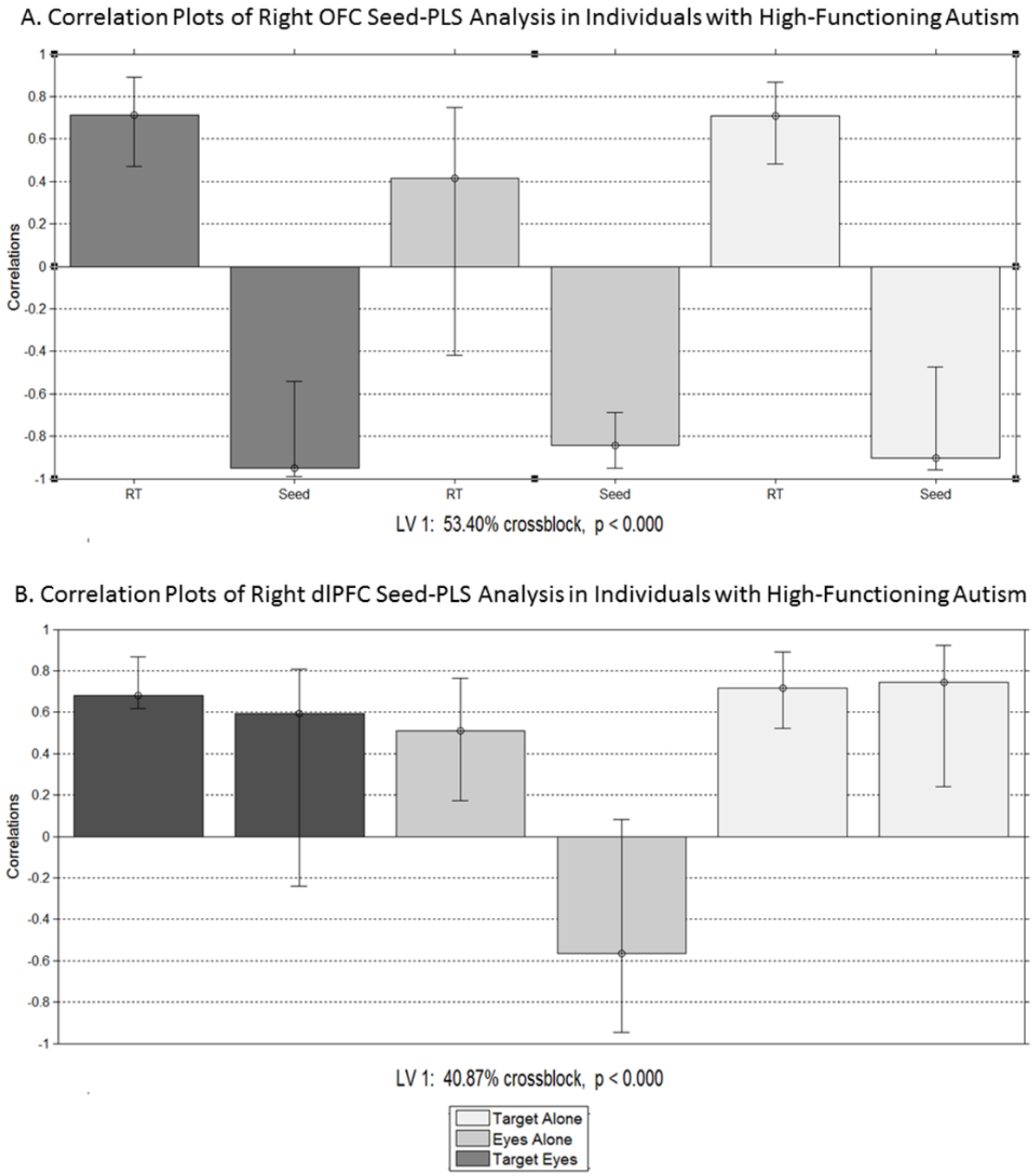

Figure 3.17. Correlation Scores from Seed-PLS Analyses in Individuals with Autism

Graph values are correlation scores for N = 13 individuals with high-functioning autism. Seed-PLS was used to identify functional neural networks associated with activity in the right OFC (A) and right dlPFC (B). Error bars represent 95% confidence intervals as determined via permutation testing.

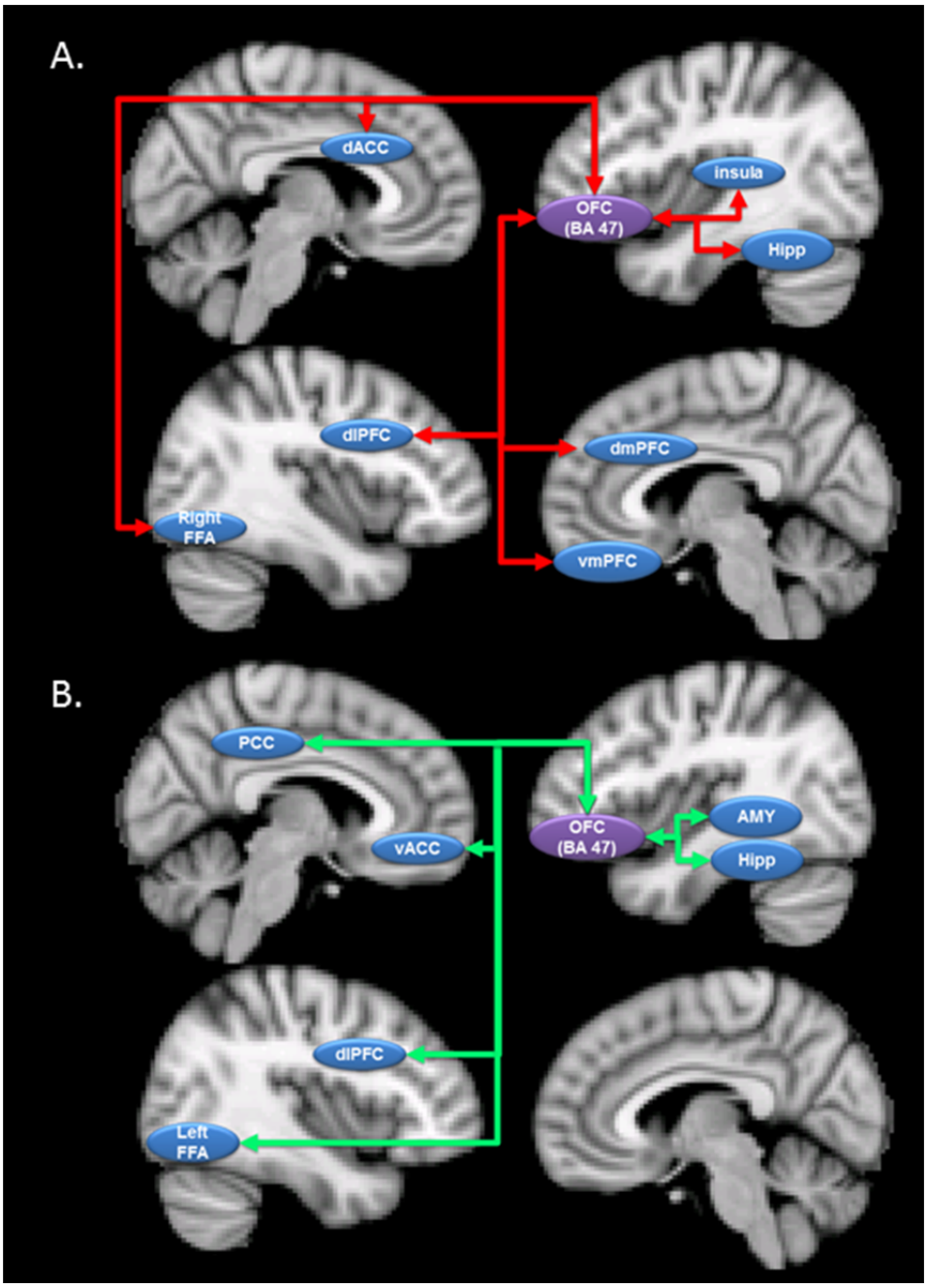

Figure 3.18. Positive and Negative Salience Networks from Right OFC Seed-PLS Analysis in Individuals with High-Functioning Autism

Functional connections in the positive salience (A) and negative salience (B) neural network coupled to the right OFC and associated with task performance (RT) in individuals with high-functioning autism Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region. Red arrows depict reciprocal correlations whereby increased activity in one region was associated with decreased activity in the paired region.

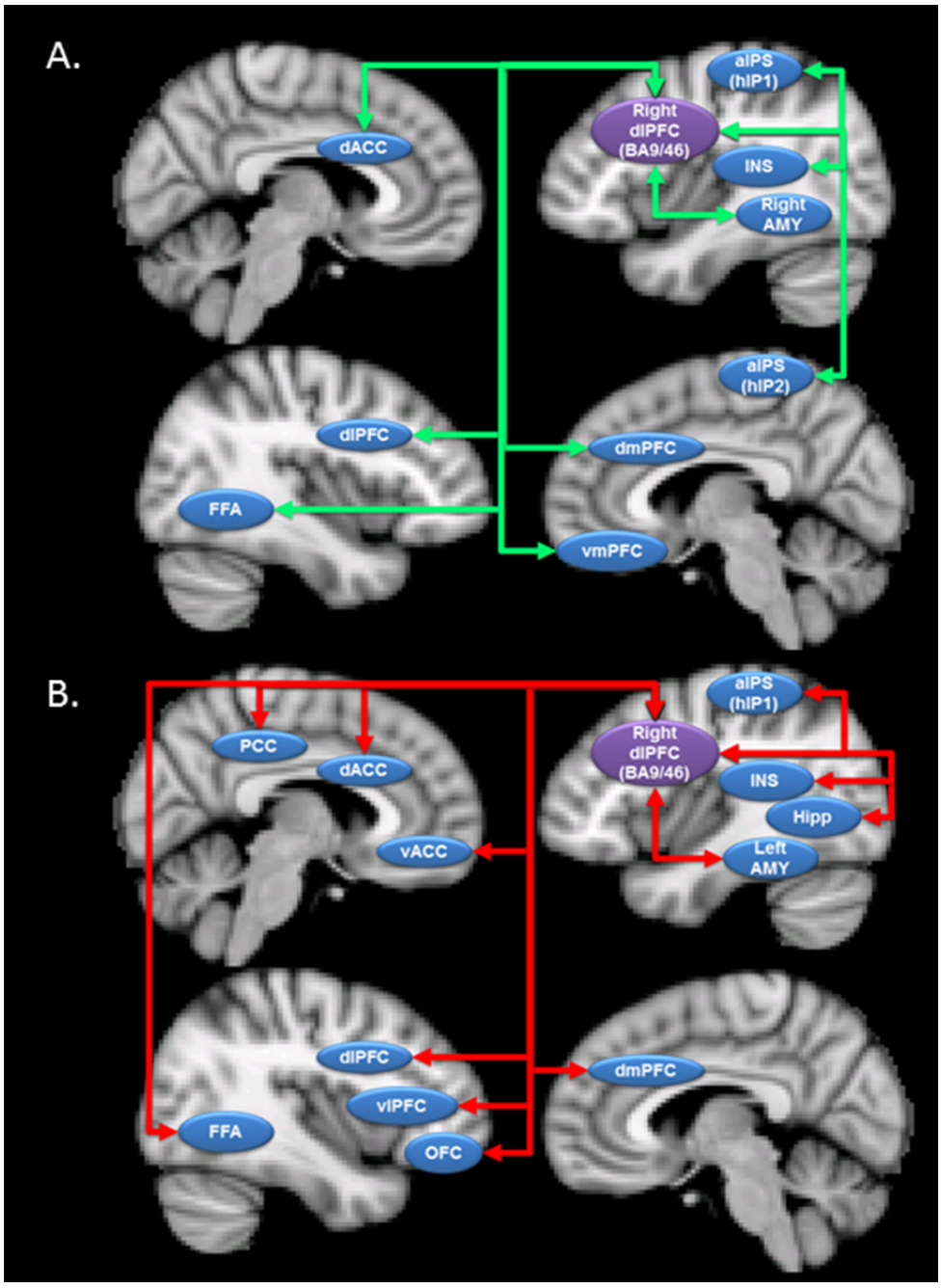

Figure 3.19. Positive and Negative Salience Networks from Right dlPFC Seed-PLS Analysis in Individuals with High-Functioning Autism

Functional connections in the positive salience (A) and negative salience (B) neural network coupled to the right dlPFC and associated with task performance (RT) in individuals with high-functioning autism. Green arrows depict positive correlations in which increased activity in one region was associated with increased activity in the paired region. Red arrows depict reciprocal correlations whereby increased activity in one region was associated with decreased activity in the paired region.

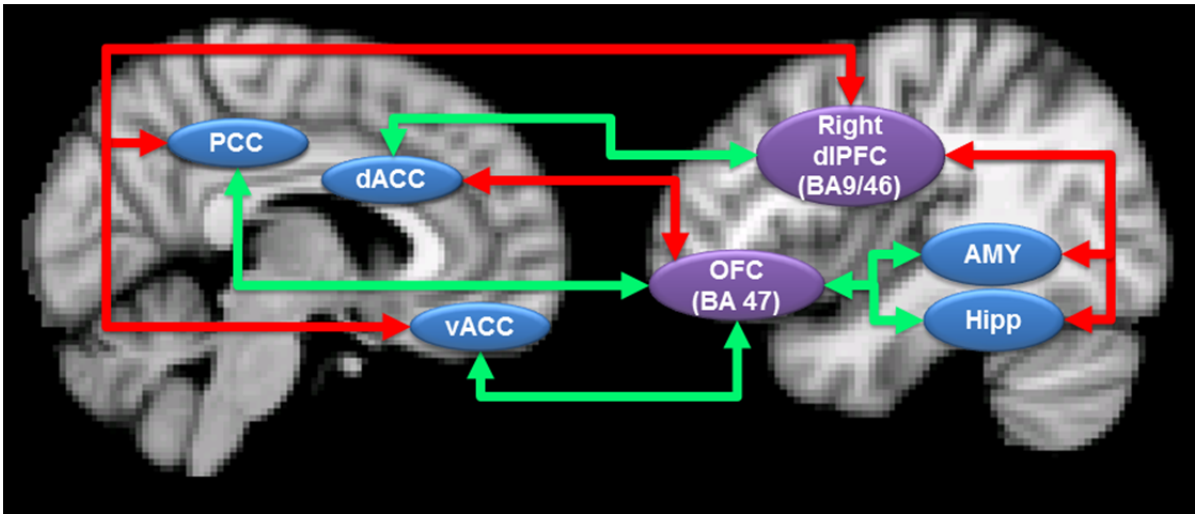

Figure 3.20. Common Functional Neural Network Associated with activity in the Right OFC and Right dlPFC in Individuals with High-Functioning Autism.

Differential activation of the right dlPFC and OFC was significantly associated with performance to the Target Eyes condition in individuals with high-functioning autism. Better performance, as measured by faster reaction time, was associated with increased activity in the OFC seed and related increased in PCC, vACC, amygdala, and hippocampus. Additionally, decreased activity in the dlPFC and dACC were also associated with faster reaction time. The opposite activation patterns was associated with slower reaction time

CHAPTER 4. DISCUSSION

Deficits in both social cognition and executive function have been documented in autism. Understanding the neural circuits that underlie these deficits will significantly advance our ability to develop new focused and biologically valid treatments. The findings from the current study provide insight into the mechanisms underlying the integration of social and executive information, which may ultimately have inform interventions that are targeted to specific brain systems associated with allowing individuals with autism to complete cognitive tasks under social conditions.

Executive functions allow for the adaptation of behavior the inhibition of inappropriate responses within the context of an ever changing social environment. As such, properly functioning executive processes are necessary for the development of socially appropriate behaviors (Bachevalier and Loveland, 2006; Jurado and Rosselli, 2007). The objective of this research was to explore the neurobiological correlates underlying the effect of an irrelevant social distracter on executive processes in a group of individuals with high-functioning autism as compared to neurotypical participants.

4.1. Target Detection is Facilitated by the Presence of Task-Irrelevant Neutral Eyes in Neurotypical Control Participants.

Increased accuracy in the neurotypical participants to the Target Eye condition as compared to the Target Alone condition suggests that pairing a target

with a socially relevant stimulus, namely an image of eyes, promotes target detection. This effect was found even when the eyes were neither task-relevant, nor predictive of whether the current trial would be a target. This extends results from previous research demonstrating that task-relevant neutral faces promote cognitive processes and suggests that the same effect is seen when the social stimuli are task-irrelevant (Dichter and Belger, 2007; Dichter et al., 2009b). Together, this suggests that social stimuli, specifically stimuli containing eyes, likely influence attentional processes that facilitate goal-directed behavior in neurotypical controls.

4.1.1. Direct Eye Gaze May Represent a "Special Class" of Stimuli that Modulates Selective Attention

The social stimuli utilized in the Social Target Detection Task were images of neutral eyes with direct gaze. The knowledge that eyes are the most attended component of faces formed the basis of the decision to focus on the eyes, as opposed to whole face stimuli. Preferential attention to the eye region of faces has been demonstrated in a number of non-human primates and a similar preference has been identified in human infants as young as two month of age (Emery, 2000; Farroni et al., 2004). In addition to identifying the presence or absence of eyes in a stimulus, the ability to determine whether gaze is directed towards or away from the viewer is also conserved across many species. It is suggested that this ability is innate based on the evolutionary importance of this distinction in prey species for which direct gaze is a very different threat cue than averted gaze (Emery, 2000).

While humans have less of a need to discriminate direct versus averted eye gaze with respect to threat by prey, the direction of gaze imparts strong

communicative information that is equally important. Thus, the evolution of the human eye is suggested to have evolved specifically to promote the transfer of communicative information based on the direction of gaze (Emery, 2000). Evidence that, even as compared to our closest non-human primate cousins, human eyes have the largest ratio of white (sclera) to dark (iris) area supports this. This increased contrast in the eyes allows for easier and more quick discrimination of the direction of gaze based on how much of the white sclera is visible (Emery, 2000). Humans are equipped with the ability to quickly analyze visual input for social relevance and to preferentially attend to direct gaze from birth. Furthermore, this process is likely facilitated by the salient sclera to iris ratio of the human eye (Farroni et al., 2002; Itier and Batty, 2009). Additionally, behavioral studies have shown that in neurotypical children and adolescents, detection of a target face is facilitated when the face has direct as opposed to averted gaze (Macrae et al., 2002; Senju et al., 2003; von Grunau and Anston, 1995). Together, this suggests that eyes, particularly eyes with gaze directed at the observer, likely comprise a "special" stimulus class that captures attention and may be subject to preferential processing. Indeed, direct gaze activates the brain's arousal system resulting in a reorientation of attention that enhances social processing and modulates ongoing and subsequent perceptual and cognitive processes (Engell et al., 2010; Senju and Hasegawa, 2005; Senju and Johnson, 2009). The ability of direct gaze to enhance social and cognitive processing, including facilitating the encoding and recognition of faces, has been demonstrated in infants as young as four months old (Farroni et al., 2002; Farroni et al., 2004; Farroni et al., 2007). Furthermore, direct gaze has been

shown to not only capture attention, but to also increase attention dwell time, delaying disengagement and enhancing processing of stimuli (George and Conty, 2008; Senju and Hasegawa, 2005). Therefore, based on behavioral findings, it is likely that the use of direct gaze stimuli in the current task enhanced attentional processing of the target stimuli in neurotypical controls.

In an effort to promote the interaction between the eye distracter and the target, the target was positioned directly between the eyes in the Target Eyes condition. It has been shown that when target and distracter stimuli are presented in the same receptive field, such as in the Target Eyes condition, the entire stimulus object is processed in parallel before individual components are separated for further processing (Desimone and Duncan, 1995; Pessoa et al., 2002a). Thus, because direct gaze stimuli modulate both cognition and attention, it is possible that combining the target with direct gaze enhanced the parallel processing of both the distracter eyes and the target. Increased accuracy to the Target Eyes as compared to when the target was presented alone suggests that this may be the case. The finding that reaction time (RT) was equivalent between these two conditions suggests that, while the eyes did enhance processing of the target stimulus, it was not likely due to the target being more readily perceivable when overlaid on the eyes. The similar reaction time further suggests that it is unlikely that the Target Eye condition was more salient than when the target was presented alone. If either of those were the case, then we would have expected faster RTs in the Target Eyes condition. Instead, it is likely that the equivalent reaction time to both the Target Alone and the Target Eyes represents the time it takes to make a behavioral switch

to a novel motor response, as opposed to being associated with attentional or target detection processes. Together this suggests that the presence of neutral eyes with direct gaze in a subset of trials resulted in the enhanced processing of those stimuli and this facilitated target detection when pairing the eyes with the target.

As previously highlighted, both top-down task-related cognitive control mechanisms and bottom-up sensory driven information are engaged and exert influence on selective attention when processing novel stimuli. However, when there is a need to overcome competition by task-irrelevant stimuli, attentional top-down feedback processes are engaged to a greater degree in order to overcome the bottom-up responses and facilitate the processing of the goal-relevant aspects of the stimulus (Corbetta and Shulman, 2002; Pessoa et al., 2002a). Therefore, it is likely that in the current paradigm top-down attentional resources were engaged in an effort to resolve the competition between the goal-directed processing of the target and the bottom-up influence of the salient direct gaze stimulus. Indeed, it has been shown that top-down feedback processes can bias the focus of attention away from salient distracters in favor of neural networks involved in processing the stimulus attributes that are most likely to facilitate goal-direct processes (Kastner and Ungerleider, 2000). Thus, while the target and distracter stimuli were initially processed in parallel, it is likely that there was subsequent recruitment of top-down attention mechanisms to enhance processing of the central fixation. Together this promoted the filtering of task-irrelevant interference by the eye stimuli and facilitated target detection (Desimone and Duncan, 1995; Pessoa, 2010; Pessoa et al., 2002a).

4.1.2. Increased Activity in Cognitive Control and Attentional Neural Networks are Associated with the Facilitation of Target Processing by Task-Irrelevant Neutral Eyes in Neurotypical Controls

The behavioral results from the Social Target Detection Task suggest that task-irrelevant direct gaze stimuli facilitates target detection in neurotypical controls. The biased competition model of attention, as well as previous research on the interaction between social stimuli and cognitive control, suggest that this process likely involves a balance between bottom-up and top-down attentional control. Specifically, as previously reviewed, the presence of eyes with direct gaze would be expected to capture bottom-up sensory driven neural networks enhancing the processing of both the eyes and the target stimuli in parallel. If this were the case, it would be hypothesized that there would be increased activation within the ventral attention stream. In particular, increased activity would be anticipated in the vlPFC which is involved in detecting and orienting to the presence of novel, salient, and behaviorally relevant stimuli, as well as in regions associated with salience assessment, such as the insula and the ACC (Bledowski et al., 2004; Corbetta and Shulman, 2002; Pessoa et al., 2002a). This attentional focus would also be expected to result in an increased neural response in extrastriate cortex, specifically in the FFC and occipital gyri, as the processing of the salient eye stimuli is enhanced. It has been shown that high-contrast salient stimuli, such as human eyes, act to enhance bottom-up stimulus driven attention processes. This biases processing in neural circuits that represent the salient stimulus at the expense of networks associated with processing other, less salient, stimuli (Kastner and

Ungerleider, 2000). In addition to the bottom-up attentional processes, top-down attentional control mechanisms would likely be engaged to promote the response to the task-relevant target stimulus and this would modulate the neural response to the eye stimuli. Specifically, previous research suggests that neural activity in response to task-irrelevant faces is enhanced if the face is superimposed on an attended shape, supporting the premise that face processing is subject to goal-relevant attentional modulation (Farroni et al., 2004; Kanwisher and Wojciulik, 2000). This top-down control would be expected to recruit the dorsal attention neural network, including the IPS, which regulates voluntary shifts in attention (Corbetta and Shulman, 2002; Marois et al., 2004; Pessoa et al., 2002a). Additional activations would be expected in regions such as the dlPFC and OFC, which are important for comparing the stimulus to mental representations of the target. The dlPFC and OFC are further associated with the updating of the salience of the stimulus based on this comparison and for the subsequent inhibition of interference by task-irrelevant stimuli competing for attentional resources (Dolcos and McCarthy, 2006; Miller and Cohen, 2001). Together, previous research supports the hypothesis that pairing stimuli that contain both direct gaze and a task-relevant target stimulus situated between the eyes orients attention and enhances processing of both the task-relevant and task-irrelevant stimuli. Additionally, it was anticipated that this would be associated with recruitment of both bottom-up and top-down attentional neural networks.

The activation maps derived from the region-based analyses in the neurotypical controls support this hypothesis by showing that pairing the eyes with

the target resulted in increased processing of both stimuli. Specifically, when the eyes were presented without a target, there was activation bilaterally in the FFC, which is involved in processing faces and is modulated by direct gaze. Interestingly, the Eyes Alone condition, while equivalent to the task-irrelevant distracter conditions in most oddball tasks, did not recruit context-updating and novelty detection neural circuitry, such as the dlPFC, vlPFC, and ACC. The lack of activations in these networks may be due to the pre-task instructions to disregard the background stimuli. Thus, it is possible that because the eyes were task-irrelevant there was no updating of the context because it does not affect task goals. It is of interest that lowering the cluster corrected threshold did not reveal any additional activation outside of extrastriate cortex. Conversely, in the Target Alone condition, there was engagement of attention and target processing circuitry, namely the left superior parietal cortex, right IPS, right precuneus, and the dACC. In summary, the Eyes Alone and Target Alone conditions successfully recruited the ventral social-affective processing and the dorsal executive control neural networks, respectively (Figure 3.2). In the Target Eyes condition, however, there was activation in both the VSAPS and the DECS networks that were activated by each the Eyes Alone and Target Along conditions, respectively. There was also evidence for increased recruitment of regions known to be involved in top-down control of attention. Specifically, there was recruitment of the left FFC in a region nearly identical to that seen in the Eyes Alone condition, as well as the right IPS, which was also active in the Target Alone condition. In addition to increased activity in these regions, there was also recruitment of the dlPFC, insula, and OFC in the right hemisphere and the insula

and vlPFC in the left hemisphere (Table 3.3, Figure 3.2). Previous research using the oddball task have identified these regions as part of the neural network associated with processing task-irrelevant distracters. This suggests that these regions were engaged to inhibit the interference by the eyes. Indeed, it has been suggested that activation of dlPFC and inferior parietal lobule to distracters is associated with top-down regulation of attention processing (Bledowski et al., 2004).

Contrast analyses further support the main effects results in the neurotypical controls. Namely, the contrast between the Target Eyes condition and the Target Alone condition (Target Eyes > Target Alone), demonstrated that the Target Eyes condition activated social neural networks, namely the bilateral FFA, to a greater extent than the Target Alone condition. Similarly, the contrast between the Target Eyes condition and the Eyes Alone condition (Target Eyes > Eyes Alone) revealed increased activation in the left superior parietal cortex, right SMG/IPS, and the right putamen extending into the insula. More interestingly, however, was the contrast between the Target Eyes condition and the conjunction of the Target Alone and the Eyes Alone conditions (Pure Social Target Condition; Target Eyes > (Target Alone and Eyes Alone). This contrast revealed that there was increased activity in the Target Eyes condition as compared to all other conditions in the left superior parietal cortex and the right FFA (Table 3.4, Figure 3.3). While activity in the dlPFC, vlPFC, and insula were not apparent in the cluster corrected Pure Social Target analysis, there was evidence of increased activation in at least the dlPFC at an uncorrected p-value of $p < 0.02$ (**Error! Reference source not found.**). Together, this suggests hat when the target was paired with the eyes, there was significantly enhanced

activation in the social processing network, specifically in the right FFA, as well as in the target-processing network, especially in the left superior parietal cortex, which was likely involved in selective attention to the target. Additionally, the more lenient uncorrected analysis suggested there might also be increased recruitment of many additional regions, notably including the bilateral dlPFC (BA9).

Based on Lavie's hypothesis of the effect of cognitive load on attention resources, the fact that there was activation in both the social and executive networks to the Target Eyes condition suggests that there was competition between the neural networks that are specialized for processing these stimuli (1995). Specifically, it is possible that while there was enhancement of the perceptual processing of the stimulus as a whole, it resulted in competition between bottom-up attention processes driven by the salient eye stimuli and top-down goal-directed processes associated with the task-relevant target. This would result in a need to recruit additional networks associated with cognitive control and selective attention to overcome the bottom-up influence of the eyes and allow the system to engage a task-relevant motor response to the target stimulus. Activations in the dlPFC, vlPFC, OFC, and insula to the Target Eyes condition, but not the Target Alone or the Eyes Alone conditions support this model. Previous research has demonstrated that top-down control in response to task-relevance can mediate the early attentional modulation imparted by direct gaze. (Senju and Johnson, 2009). It is possible that in the current task, this top-down control was imparted by the increased activity in the dlPFC, vlPFC, and the OFC, all of which are involved in integrating social and executive information and which have been found to inhibit distraction imparted by

task-irrelevant social stimuli (Barbas et al., 2010; Beer et al., 2006a; Dolcos and McCarthy, 2006; Fichtenholtz et al., 2004; Pessoa, 2008; Yamasaki et al., 2002). Furthermore, it is known that the regions activated by the Target Eyes condition in the neurotypical controls, such as the vlPFC, dlPFC, and insula, as well as the IPS are involved in top-down and bottom-up attentional control (Engell et al., 2010).

Much of the research on the interaction between the dorsal executive control and the ventral social neural networks has focused on cognitive interference associated with emotional face stimuli. When the distracting stimuli contain emotional information (generally negatively valenced, e.g. sadness, fear, and anger), there is evidence for an over-riding of the executive neural circuitry that results in a disruption of ongoing cognitive processes, thus interrupting behavioral output (Dolcos et al., 2008; Dolcos et al., 2006; Dolcos and McCarthy, 2006; Fichtenholtz et al., 2004; Wang et al., 2005; Yamasaki et al., 2002). The neutral eyes in the current task has produced an opposite effect, facilitating processing of the target. This replicates findings from other behavioral and imaging studies utilizing neutral face stimuli and thus is not likely to be specific to the current task. Instead, it is possible that while similar neural circuitry is activated in response to both emotional and neutral social distracter stimuli, the influence that these have on processing is different based on the differential information that they convey (i.e. communicative versus threat) or the differential pathways from the amygdala that they activate. One potential explanation for this is the role of motivational states on cognitive control. Research on this interaction has suggested that there is a distinction between stimuli that induce approach versus avoidance motivated states and the influence of these

two states on cognitive control are different. Specifically, approach related motivational states are associated with facilitation of tasks that target the left PFC, such as verbal working memory tasks, whereas withdrawal motivational states are associated with facilitation of tasks that target the right PFC, such as spatial working memory paradigms (Gray, 2001). There is evidence suggesting that neutral faces with direct gaze elicit approach-related motivational behavior. On the other hand, negatively valenced emotional faces (e.g. expressing fear) such as those used in many of the previous studies exploring the role of emotion in regulating cognition, elicit withdrawal-related motivational behavior (Gray, 2001; Hietanen et al., 2008). Thus, while not a focus of the current study, this dichotomy between approach and withdrawal motivational states supply an interesting explanation for how the same neural systems can produce conflicting results with respect to the effects of emotional and neutral social stimuli on cognitive control and thus should be considered in future studies.

4.2. Task-Irrelevant Images of Eyes Compete with Processing of the Goal-Relevant Aspects of Stimuli in Individuals with High-Functioning Autism

While many previous studies have established anatomical and functional differences in neural circuitry associated with social cognition and cognitive control in individuals with autism, these studies have almost exclusively examined these networks in isolation. Previous research from Dichter and colleagues (Dichter and Belger, 2007; Dichter et al., 2009a) has provided clues to the functional alterations associated with the difficulty that individuals with autism exhibit when utilizing social

cues, specifically eye gaze, to complete a cognitive task. However, to date no study has addressed the question of whether the presence of a social context that is irrelevant to the cognitive task will also result in altered neural network activity in individuals with autism.

Results from the current study suggest that, similar to neurotypical controls, target detection in individuals with high-functioning autism was facilitated by the presence of task-irrelevant eye stimuli; however, the level of this facilitation was significantly lower than that of neurotypical controls as evidenced by significantly worse accuracy on the Target Eyes condition. The finding that task-irrelevant neutral eyes facilitated target detection in individuals with autism was surprising in light of a number of studies demonstrating that faces, and especially eyes, are not salient enough to capture the attention of individuals with autism (Dawson et al., 2004a; Klin et al., 2002; Neumann et al., 2006; Riby and Hancock, 2009; Swettenham et al., 1998). The difference between these previous studies and the current oddball task, however, is that in the current task the individuals with autism were forced to foveate towards the eyes in order to identify whether the fixation, which was located between the eyes, was a target or non-target. Instead, the previous research has focused on either attention to eyes during an emotion discrimination task (Neumann et al., 2006), on attentional shifts and interactions with an interviewer (Dawson et al., 2004a; Swettenham et al., 1998), or on attention to faces within the context of a larger scene (Klin et al., 2002; Riby and Hancock, 2009). Thus, while it is likely that social stimuli, and particularly eyes, do not capture the attention of individuals with autism when they are part of a scene or a social

encounter, they become salient when the individual with autism attend to the eyes and, in the current study, they compete with the processing of goal-relevant stimulus properties. This supports previous findings of increased arousal associated with attention to direct gaze stimuli in individuals with autism and suggests that this increased arousal may occur even when the eyes are task-irrelevant and may interfere with processing of task-relevant aspects of the stimuli (Dalton et al., 2005; Joseph et al., 2008; Kylliainen and Hietanen, 2006).

While direct gaze stimuli did facilitate target processing in the individuals with autism, there was a behavioral tradeoff to having the direct gaze stimuli in the paradigm. Specifically, the task-irrelevant eyes increased the number of false alarm errors in response to the non-target Eyes Alone condition. This suggests that the individuals with autism had a decreased ability to discriminate between the target and non-target stimuli when paired with the task-irrelevant eyes. This was in agreement with Sokhadze and colleagues (2009), who hypothesized aberrant attention allocation and reduced discrimination of task-relevant versus task-irrelevant stimuli in individuals with autism. In the context of the current study, this suggests that individuals with autism were less able to filter interference from the eye stimuli. Previous research suggests that attention to social stimuli, particularly direct gaze, increases arousal in individuals with autism. Thus, it is possible that an increased arousal to the task-irrelevant eyes may have decreased the ability of the participants with autism to distinguish between when the stimuli containing the eyes was associated with a target or a non-target response (Dalton et al., 2005; Joseph et al., 2008; Kylliainen and Hietanen, 2006). Indeed, it is suggested that attention in

individuals with autism was engaged more as a means to control general arousal, than as a tool to filter task-irrelevant information or facilitate detection of behaviorally relevant stimulus attributes. Thus, while irrelevant distracters are filtered at early perceptual stages by neurotypical participants, the filtering of the relevant stimulus from an "indiscriminately amplified background" in individuals with autism occurs at a later stage that is likely associated with inhibitory processes (Belmonte and Yurgelun-Todd, 2003). Therefore, this suggests that decreased discrimination in the individuals with autism may have been associated with attentional processes being engaged to control arousal to the eyes. This was likely at the expense of focusing attention on task-relevant stimulus attributes, thus impairing inhibition of interference by task-irrelevant distracters.

4.2.1. Increased Recruitment of Cognitive Control and Attentional Neural Networks Resolves Competition of Task-Irrelevant Eyes with Processing of the Goal-Relevant Aspects of Stimuli in Individuals with High-Functioning Autism

One potential explanation for the increased interference by the eye stimuli is that there was reduced connectivity between the frontal and limbic networks in individuals with autism, such that frontal cognitive control networks were unable to inhibit the limbically mediated arousal to the task-irrelevant eye stimuli. This would result in an inability of individuals with autism to tune attentional control networks toward processing only the goal-relevant aspects of the stimuli. Functional imaging results support this suggestion. Specifically, contrast and region of interest analyses revealed that individuals with autism as compared to the neurotypical controls

displayed increased activity in the right FFC, as well as the dACC and PCC when making correct responses to the Eyes Alone condition. As already reviewed, previous research suggests that the dACC is involved in signaling the need for increased engagement of cognitive and attentional control circuitry, whereas the PCC works in concert with the dACC to facilitate selective attention to goal-relevant stimuli and is involved in the suppression of distraction (Barbas, 2000; MacDonald et al., 2000; McRae et al., 2010). Thus, increased activation of the dACC and PCC in the individuals with autism to the Eyes Alone condition suggests that these participants required greater recruitment of cognitive control processes, potentially in response to increased FFC activation, in order to make a correct behavioral (non-target) response. Importantly, this increased need for cognitive control was not associated with a need to switch to a novel motor response because the Eyes Alone condition requires the same behavioral response as standards. Thus, this increased cognitive control cannot be attributed to a need to inhibit a prepotent response. As such, the increased cognitive control processes engaged by individuals with autism to the Eyes Alone condition likely represents a need to tune frontal and parietal networks, focusing attention on the task-relevant fixation point and away from the distracting task-irrelevant eye stimuli.

While both the Eyes Alone and Target Eyes conditions require inhibition of interference by the task-irrelevant eye stimuli on the ability to process the fixation point as a target or non-target stimulus, the Target Eyes condition has the added burden of a behavioral shift requiring the inhibition of a prepotent response. The trend for decreased accuracy to both target conditions in individuals with autism

supports previous research highlighting the difficulties individuals with autism have with inhibition of a prepotent response (Kana et al., 2007; Shafritz et al., 2008; Solomon et al., 2008; Solomon et al., 2009). Thus, if there was increased recruitment of cognitive control resources in individuals with autism in order to overcome the interference by the eye stimuli in the Eyes Alone condition, then it would be expected that the Target Eyes condition would require even greater involvement of inhibitory control networks. Specifically, it would be expected that in order to make a correct response to the Target Eyes condition, individuals with autism would require greater involvement of neural networks underlying the ability to inhibit distraction, allocate attention towards goal-relevant stimulus properties, and the prepotent motor response. Indeed, the functional neuroimaging data support this assumption in that, while the neurotypical participants displayed activations in right lateralized OFC, dlPFC, and pIPS, the individuals with autism displayed bilateral activations in these regions.

Previous research has highlighted the differential roles of the left and right dlPFC in processing distracting information, with the right dlPFC activating in response to processes underlying identification of the distracting stimulus and the left dlPFC driving the influence of the neurofunctional differences on behavioral responses (Dolcos et al., 2008). Thus, while activity in the right dlPFC may be associated with the increased control required to inhibit distraction by the task-irrelevant eyes in both groups, the increased left dlPFC activation in the individuals with high-functioning autism may be due to their increased difficulty with inhibiting the prepotent response and initiating the appropriate button press. A number of

studies have highlighted the role of the left dlPFC in inhibiting a prepotent response in favor of a novel, goal-relevant behavioral output (Barber and Carter, 2005; MacDonald et al., 2000; Shafritz et al., 2005). Furthermore, it is suggested that in addition to exerting top-down control over the prepotent motor response, the dlPFC also works in concert with the IPS to facilitate shifts in behavioral responses by driving the attentional resources towards the task-relevant properties of a stimulus, thus promoting target detection (Kirino et al., 2000; McCarthy et al., 1997; Shafritz et al., 2005). Therefore, in addition to its role in inhibition of prepotent responses, the increased recruitment of left dlPFC in concert with the left IPS in the individuals with autism may be further associated with controlling the allocation of attentional resources away from interference by the task-irrelevant eye stimuli and towards goal-relevant stimulus attributes. Previous research has highlighted that interactions between the dlPFC and the IPS are involved in the top-down control of attention required to inhibit interference by salient task-irrelevant information (Bledowski et al., 2004; Brazdil et al., 2007; Dolcos and McCarthy, 2006). Additionally, it has been suggested that the attentional filtering of task-irrelevant information in individuals with autism occurs at later processing stages than in neurotypical controls and this is likely associated with inhibitory control processes within the intraparietal cortex (Belmonte and Yurgelun-Todd, 2003). Together this suggests that left lateralized activity in both the dlPFC and the IPS in the individuals with autism, but not in the neurotypical controls, was likely associated with difficulties individuals with autism have with inhibiting prepotent responses, as well as an increased need to allocate resources towards inhibiting interference by the salient, but task-irrelevant, eyes.

In addition to the left dlPFC and IPS, the left OFC was also activated more in the individuals with autism as compared to the neurotypical controls in response to the Target Eyes condition. This increased OFC activation further supports the hypothesis that heightened arousal may be associated with attention to direct gaze stimuli, even in a task in which the eyes were task-irrelevant. Furthermore, it is possible that this arousal interferes with processing of task-relevant aspects of the stimuli. Indeed, the OFC, along with the amygdala and the ventral striatum, has been shown to play an essential role in encoding the affective valence of stimuli (Bachevalier and Loveland, 2006; Ochsner, 2008). Thus, it would be expected to be activated in response to stimuli that are highly arousing. Additionally, the OFC is a primary node within the alerting network comprised of connections between the sensory association cortices (e.g. FFA), the amygdala, and anterior cingulate cortices. As previously highlighted, increased arousal in response to a stimulus is associated with activation of inhibitory GABAergic innervations from the posterior OFC to amygdala, which act to disinhibit the hypothalamus, initiating a cascade of responses that include increased heart rate and perspiration (Barbas, 2007). Thus, increased activation in the left OFC to the Target Eyes condition was consistent with previous research suggesting that attention to eyes is associated with increased arousal (Dalton et al., 2005; Joseph et al., 2008; Kylliainen and Hietanen, 2006). Additionally, it supports the hypothesis that, in the context of the current task, the increased arousal results in a decreased ability of individuals with autism to filter interference from the eye stimuli and that this contributes to their decreased ability to

distinguish between when the stimuli containing the eyes was associated with a target or a non-target response

In addition to its role in assessing the salience of stimuli, the OFC is also important for incorporating social information into decision making when appropriate and recruiting cognitive control mechanisms to inhibit it when it is not relevant to current goals (Beer et al., 2006b; Casey et al., 2002; Garavan et al., 2002). This inhibition has been jointly linked to the OFC, dlPFC, and lateral parietal cortex, with the dlPFC and OFC biasing attentional processes meditated by the lateral parietal cortex towards task-relevant stimulus features (Barbas et al., 2010; Dolcos and McCarthy, 2006; Miller and Cohen, 2001). Furthermore, anatomical connections between frontal and parietal cortices allow for the integration of selective attention signals that engage inhibitory connections between the frontal cortices, particularly the OFC, and social processing regions, such as the amygdala and vlPFC. This is further associated with the inhibition of interference by task-irrelevant social information (Banks et al., 2007; Blair et al., 2007; Ochsner and Gross, 2005). Thus, the lack of left vlPFC activity in the individuals with autism may be a consequence of top-down control processes imparted by the increased left OFC, dlPFC, and pIPS activity in the individuals with autism.

4.3. Differential Connectivity Patterns Underlie the Neural Networks Associated with the Integration of a Target with Task-Irrelevant Eyes in Both Individuals with Autism and Neurotypical Controls – An Exploratory Analysis

Understanding how single regions within a network are differentially activated in individuals with autism as compared to neurotypical controls provides an important first step towards elucidating the neurofunctional underpinnings of social and cognitive deficits in autism. However, discrete regions of the brain do not function in isolation, but instead work in concert with a broader network of regions. Thus, in addition to the region-based functional imaging analyses already highlighted, exploratory functional connectivity analyses further investigated network level differences in individuals with autism as compared to neurotypical controls.

Previous research has led to the hypothesis that autism is characterized by local over-connectivity and long-range under-connectivity, with fronto-parietal, fronto-temporal, and fronto-limbic connections being especially aberrant (Geschwind and Levitt, 2007). As already highlighted, region-based results from the current study support this assertion. Specifically, it is suggested that dysregulation of fronto-limbic connections contributed to the decreased ability of individuals with autism to discriminate between target and non-target event when presented with task-irrelevant eye stimuli. The primary finding from the region-based analyses suggests that individuals with autism relied more on cognitive control neural circuitry, specifically in the left hemisphere, to successfully discriminate target and non-target stimuli. While this increased activation was found in the left hemisphere in

individuals with autism, both groups displayed activations in the dlPFC and OFC in the right hemisphere. Thus, exploratory functional connectivity analyses focused on the nodes that were activated by both groups to explore how differential engagement of these nodes contributed to behavioral output. An additional functional connectivity analysis was run on a seed from the left vlPFC, which was activated in the neurotypical controls, but not the individuals with autism. The decision to also incorporate this seed was founded in literature suggesting that, in neurotypical participants, the ability to overcome interruption of goal-directed processes is associated with co-activation of the left vlPFC and right dlPFC. Specifically, these regions have been shown to work together to inhibit distraction by affective information at the same time as parietal attentional regions act to direct the attentional resources away from the distracting stimulus and towards the task-relevant information (Dolcos et al., 2008; Dolcos et al., 2006; Dolcos and McCarthy, 2006; McRae et al., 2010). This compliments the finding of increased activity in these regions in the neurotypical participants in the current study. Furthermore, the differential recruitment of networks associated with these regions may partially underlie the behavioral differences between individuals with autism and neurotypical controls.

While there is clear importance in understanding group differences in the functional connectivity patterns of each seed independently, the focus of the current exploratory analysis was to compliment the regional findings from region-based analyses by investigating how these nodes differentially interact with their broader neural networks in the individuals with autism as compared to the neurotypical

controls. Thus, the current discussion will focus primarily on the comparison of the overlap between the functional networks in each of the groups, as opposed to breaking down each network on its own.

Three main findings emerged from the comparison of the functional networks associated with the dlPFC and OFC seeds in the individuals with autism to the networks functionally connected to the dlPFC, OFC, and vlPFC seeds in the neurotypical participants. The first finding was that in the neurotypical participants, there was only a single direction of functional connections with the right OFC (i.e. there was only a positively correlated network in the neurotypical group) whereby all regions in the network identified in the neurotypical participants were positively correlated with activity in the right OFC (Figure 3.5 and Figure 3.18). On the other hand, in the individuals with autism there was both a positive and a negative network associated with activity in the right OFC. This may suggest that the right OFC in the individuals with autism was regulating more or was under greater regulation by other regions than it was in the neurotypical participants. This may have been in response to lack of involvement of the left vlPFC in regulating the interaction between the neural networks. More likely, however, these results may reflect the inevitable fact that the group of participants with autism was more heterogeneous than the neurotypical participants. This would result in increased variability in how the OFC interacted with the broader neural network in the group with autism. Thus, in some participants with autism the positive salience OFC network was more functionally connected in response to the Social Target Detection Task, whereas in other

participants with high-functioning autism the negative salience OFC network contributed to the task to a greater degree.

The second finding was that there were more nodes displaying overlap between the right OFC and right dlPFC in the individuals with high-functioning autism than in the neurotypical controls (Figure 3.20). Specifically, both groups display overlap between the dlPFC and OFC networks at the PCC, however there were no other overlapping regions between these networks in the neurotypical controls. On the other hand, the functional networks in the individuals with autism had additional overlapping clusters in the dACC, vACC, amygdala, and hippocampus. However, if the vlPFC connectivity is taken into account when comparing the regions that overlapped in the neurotypical participants to that of the individuals with autism, there was striking convergence between the two networks. Specifically, in the individuals with autism, there was dlPFC and OFC networks were both functionally connected to the dACC and vACC. One the other hand, in the neurotypical participants the dlPFC and OFC networks did not overlap at the dACC and vACC, however, these regions were shared between the functional networks associated with the OFC and vlPFC seeds. Interestingly, while there was clear overlap between the OFC and dlPFC in the amygdala and hippocampus of individuals with autism, there was no equivalent overlap in the neurotypical network.

The final finding was that, in addition to the differences in the networks that were activated by the individuals with autism as compared to the neurotypical controls, there were also differences in the direction of activation in these networks and the effect of this pattern on behavioral performance. Specifically, faster reaction

time to the Target Eyes in the individuals with autism mapped onto a neural network in which increased activity in the right OFC seed was associated with increased activity in a number of regions, including the PCC, vACC, amygdala, and hippocampus. Furthermore, increased activity in this network was associated with decreased activity in the right dlPFC seed. On the other hand, faster reaction time to the Target Eyes in the neurotypical participants mapped onto a neural network in which decreased activity in the right OFC and vlPFC seeds was associated with decreased activity in the PCC, vmPFC, and right medial OFC. This was further associated with increased activity in the right dlPFC seed. Thus, in individuals with autism, faster reaction time was correlated with the increased activity in the right OFC and decreased activity in the right dlPFC, whereas the opposite was true for neurotypical participants.

The finding that the right dlPFC and OFC activation was differentially associated with behavioral output in individuals with autism as compared to neurotypical controls was unexpected. However, when considered in the context of the results already discussed, it is likely that these functional connectivity findings were rooted in the more basic differences in cognitive control, inhibition of prepotent response, and inhibition of interference by the task-irrelevant eyes that have already been highlighted. Previous research suggesting differential roles for the dlPFC, OFC, and vlPFC in cognitive control processes further supports this conclusion. Specifically, Casey and colleagues (2005) have suggested that cognitive control processes, especially those involved in inhibitory control, can be subdivided into subdomains of stimulus selection, response selection, and response execution.

Additionally, they have identified that these subdomains of cognitive control can be mapped onto dissociable frontal neural networks. Specifically, they suggest that stimulus selection, which refers to the processes associated with inhibiting interference over distracting information in favor of processing goal-relevant stimulus attributes, is associated with activity in the dlPFC. On the other hand, the processes associated with exerting control over competing response alternatives (response selection) and with inhibiting a task-inappropriate prepotent motor response (response execution) are associated with activity in the lateral and medial OFC, respectively (Casey, 2005). Thus, it is possible that the differential behavioral consequences associated with the regulation of the OFC and dlPFC and their respective functional networks may be associated with the differences in the inhibitory control requirements between the individuals with autism and the neurotypical controls. Indeed, as highlighted above, the behavioral and region-based imaging findings suggest that both the neurotypical participants and the individuals with autism likely engage the right dlPFC and OFC networks in an effort to overcome the bottom-up attentional capture of the salient direct gaze stimuli. However, in addition to needing to recruit cognitive control processes to inhibit distraction by the task-irrelevant direct gaze stimuli, the individuals with autism were also faced with an increased difficulty inhibiting the prepotent motor response associated with the behavioral switch to the target stimulus. Thus, in the neurotypical participants the finding that faster reaction time to the Target Eyes was related to increased activity in the dlPFC and an associated decrease in activity in the broader neural network, including the OFC and the vlPFC, suggests that the

neural networks functionally connected to the right dlPFC were likely associated with stimulus selection processes. Previous research has highlighted the role of the OFC and the vlPFC in detecting and orienting to the presence of novel, salient and behaviorally relevant stimuli, and to a need to inhibit interference by competing stimulus properties (Bledowski et al., 2004; Corbetta and Shulman, 2002; Pessoa et al., 2002a). Therefore, it is likely that these regions were engaged early in processing in response to the direct gaze stimuli in the neurotypical controls. However, because the direct gaze was not task-relevant, the dlPFC was engaged to inhibit the activity in these regions and their associated networks, thus supporting top-down control of the salience detection network in favor of attentional focus on the task-relevant stimulus attributes. As such, increased activation in the right dlPFC of neurotypical controls results in decreased activity in the broader network comprised of the OFC, vlPFC, cingulate cortex, and vmPFC and this was further associated with facilitation of target detection, as evidenced by faster reaction time to the Target Eyes condition.

On the other hand, the functional connectivity analysis in the individuals with autism suggested that faster reaction time to the Target Eyes was associated with increased activity in a functional network that was correlated with increased activity in the right OFC and decreased activity in right dlPFC. Thus, it is possible that the right lateralized network in the individuals with autism was involved in processes underlying response selection and response execution, such that the activation pattern identified in this network was recruited in an effort to overcome the strong competition from the prepotent motor response. In addition to this, however, there

was also evidence for a role of this network in inhibiting the effects of increased arousal by the direct gaze stimuli. Specifically, in the individuals with autism there was clear overlap between the OFC and dlPFC networks in the amygdala and hippocampus, whereas there was no equivalent overlap in the neurotypical network. Thus, it is possible that the modulation of this network by the salient eye stimuli was driven by the amygdala, which has direct connections to both the OFC and the dlPFC, and this resulted in the affective modulation of cognitive and attentional control (Barbas et al., 2010; Pessoa et al., 2002a). Indeed, as reviewed in the introduction, it has been suggested that the amygdala plays an important role in the integration of sensory information and projects that information to lateral PFC, ACC, and OFC (Pessoa, 2008, 2010). Additionally, strong reciprocal connections between sensory cortices, the amygdala, and the OFC allow these regions to not only integrate highly processed sensory information, but to also send feedback information about the behavioral and social significance of the stimulus to the sensory cortex. This results in a biasing of later-stages of perceptual processing of the stimulus (Pessoa, 2008; Pessoa et al., 2002a). Finally, there exists a pathway from the amygdala through the thalamus to the OFC, which allows the amygdala and OFC to flexibly update the significance of stimuli as related to current goals, which in turn can drive attentional focus away from distracters and towards salient or goal-directed stimuli (Barbas et al., 2010). Thus, the finding that functional connections between the dlPFC, OFC, amygdala, and cingulate cortex were associated with regulation of behavioral response to the Target Eyes condition in the individuals with autism supports the conclusion that the eyes were arousing to the

participants with autism. Furthermore, the regulation of this arousal was directly associated with behavioral performance on the task.

Finally, it is of interest to note that the neural networks associated with activity in the individuals with autism and the neurotypical controls both converge at the dACC and the PCC. This suggests that, while activity in these networks were likely associated with differential inhibitory processes, they were both associated with engagement of cognitive and attentional control circuitry. Thus the dlPFC and OFC networks in both groups played a critical role in facilitating selective attention to goal-relevant stimuli, as well as in suppressing interference by distracters.

4.4. Conclusions, Limitations, and Future Directions

In summary, behavioral and region-based neuroimaging results from the Social Target Detection Task suggest that task-irrelevant direct gaze enhances attentional processing of targets in neurotypical controls. On the other hand, while behavioral results suggest that the eyes also facilitated target processing in the individuals with autism, the effect was smaller than that seen in the neurotypical control group. This was evidenced by significantly worse accuracy in the individuals with autism to the Target Eyes as compared to the neurotypical controls. While non-significant, there was also a trend for decreased accuracy to all targets in the individuals with autism. This was likely associated with previously identified deficits in inhibition of prepotent response. Investigation of the effect of the task-irrelevant eye stimuli on the ability of participants to discriminate between target and non-target stimuli further revealed that the task-irrelevant eyes also increased the

number of false alarm errors individuals with autism made in response to the non-target Eyes Alone condition. A similar discriminability trade-off was not found in the neurotypical controls. Thus, behavioral results suggest that individuals with autism were faced both with increased difficulty inhibiting a prepotent response to target stimuli, as well as a decreased ability to filter interference from the eye stimuli.

Neuroimaging results support the conclusion that individuals with autism were faced with increased cognitive demand from both the increased interference of the eye stimuli, as well as an increased difficulty with inhibiting prepotent responses. Specifically, decreased discriminability of target and non-target stimuli when paired with direct gaze was associated with increased activity in the dACC and PCC in individuals with autism as compared to controls. Because all of the neuroimaging analyses were run on correct only trials, this suggests that successful discrimination of an Eye Alone stimulus as a non-target event relied on increased cognitive and attentional control processes in the individuals with autism. Additionally, both groups displayed increased activation to the Target Eyes condition in right dlPFC, OFC, and parietal cortices. Based on the biased competition model of attention, as well as previous research on the interaction between social stimuli and cognitive control, this activity was likely associated with creating a balance between bottom-up and top-down attentional control processes required to focus attention away from the salient, but task-irrelevant eye stimulus and towards the task-relevant target. However, while this activation was isolated to the right hemisphere in the neurotypical controls, individuals with autism activated this network bilaterally. Increased activity in both the left dlPFC and the left IPS in the individuals with autism, but not in the

neurotypical controls, was likely associated both with difficulties individuals with autism have in inhibiting prepotent responses, as well as increased interference by the task-irrelevant eyes. Additionally, increased activation in the left OFC to the Target Eyes condition was consistent with previous research suggesting that attention to eyes was associated with increased arousal. Furthermore, the OFC is also associated with inhibition of interference by social information when it is not relevant to current goals. The inhibitory role of the OFC has been linked to its interactions with the dlPFC and lateral parietal cortex, with the dlPFC and OFC biasing attentional processes meditated by the lateral parietal cortex towards task-relevant stimulus features (Barbas et al., 2010; Dolcos and McCarthy, 2006; Miller and Cohen, 2001). Finally, the finding of a lack of left vlPFC activity in the individuals with autism despite activation of this region to the Target Eyes in the neurotypical controls may be a consequence of top-down control processes imparted by the increased left OFC, dlPFC, and pIPS activity in the individuals with autism.

Exploratory analysis of functional connectivity suggest that, in addition to increased recruitment of cognitive control networks in the individuals with autism, functional connectivity within the regions that were activated by both groups, specifically the right OFC and right dlPFC, were differentially associated with task performance. Specifically, in the individuals with autism, faster reaction time was correlated with activity in neural networks associated with increased activity in the right OFC and decreased activity in the right dlPFC, whereas the opposite was true for neurotypical participants. This suggests that despite similar activation patterns,

these regions were likely playing different, yet complimentary roles in both groups. Specifically, research suggests that the dlPFC is more associated with the stimulus selection function of cognitive control, whereas the OFC is more associated with response selection and execution. Thus, in the neurotypical participants the finding that faster reaction time to the Target Eyes was related to increased activity in the dlPFC and an associated decrease in activity in the broader neural network, including the OFC and the vlPFC, suggests that the neural networks functionally connected to the right dlPFC were driving stimulus selection processes in this group. More specifically, increased activation in the right dlPFC of neurotypical controls resulted in decreased activity in the broader network comprised of the OFC, vlPFC, cingulate cortex, and vmPFC and this was associated with facilitation of target detection, as evidenced by faster reaction time to the Target Eyes condition. On the other hand, the functional connectivity pattern in the individuals with autism suggests that the right lateralized network in these participants was involved in response selection and response execution processes associated with the inhibition of a prepotent motor response. In addition to this, the finding that functional connections between the dlPFC, OFC, amygdala, posterior and anterior cingulate cortex were associated with regulation of behavioral response to the Target Eyes condition in the individuals with autism, but not neurotypical controls, was evidence that the eyes were arousing to the participants with autism. Differential activation within these networks was further associated with the regulation of this arousal and thus was directly associated with behavioral performance on the task.

In conclusion, results from this work suggest that the presence of task-irrelevant neutral eyes increased attention to the stimulus in both neurotypical controls and individuals with autism. However, in neurotypical participants this facilitated target detection and tuned attention such that they were better able to discriminate between target and non-target events. On the other hand, the eye stimuli facilitated target detection in individuals with autism, but impaired their ability to discriminate between target and non-target events. Additionally, the ability of neurotypical controls to better discriminate between target and non-target events was likely due to the engagement of frontal cognitive control and selective attention circuitry, which facilitates attention to and enhances processing of task-relevant information while filtering distracting irrelevant sensory input. Conversely, there was a pattern of differential connectivity between frontal and limbic circuits in the individuals with autism, such that the frontal regions were less efficient at inhibiting the limbically mediated response to the eyes. This resulted in a decreased ability of the individuals with autism to filter interference by the task-irrelevant eye stimuli. This further contributed to decreased tuning of attentional control processes, resulting in a decreased ability to discriminate between target and non-target stimuli when those stimuli were paired with task-irrelevant eyes.

As reviewed in the introduction, there are several theories to the developmental mechanisms underlying the difficulties individuals with autism have with processing social information, particularly information garnered from gaze cues. Of the theories reviewed, both assume functional dysregulation of the amygdala early in development, which result in a lack of attention to the social stimuli in

infancy. This was further associated with decreased experience with social information, which can explain decreased activation in face sensitive regions, specifically the FFA. Additionally, both of these hypotheses may help explain why individuals with autism have difficulty with cognitive processes within a social context. Specifically, increased arousal to social stimuli may result in a commandeering of neural resources away from executive networks decreasing the accuracy of the individuals with autism on the task. In a similar fashion, if there is a lack of specialization of the neural circuitry involved in processing social information and an individual with autism is tasked with sorting through both social and executive information simultaneously, it may tax the attention systems and increase the cognitive demand associated with the task. While the current study was not able to disentangle these developmental mechanisms, it does add to the evidence suggesting that increased response to social stimuli may result in a commandeering of neural resources away from executive networks making it more difficult for individuals to perform the executive task.

The current research provides a first glimpse at the effects of a task-irrelevant social context on cognitive processing in individuals with autism. However, the results need to be interpreted with caution based on some fundamental limitations with task-design and data analysis. The primary limitation of the current study was the lack of a comparison condition that includes salient, but non-social task-irrelevant stimuli. Without this comparison, it was not possible to say with certainty whether the current effects were due to the social-relevance of eyes with direct gaze, or whether it was an effect of a generally salient context. Additionally, it is

possible that events containing the task-irrelevant eyes were perceptually different enough from events without the eyes to induce a distraction effect. The finding that the participants with autism had worse discrimination between target and non-target conditions that included task-irrelevant eyes, whereas there was no loss of discriminability in the neurotypical group, suggests it was not due to perceptual differences in the stimuli. However, it was impossible with the current task design to predict whether this same effect would not be found in response to any salient distracter condition. Thus, future studies will need to include an additional set of non-social comparison conditions.

With respect to data analysis, because the accuracy in both groups, especially in the individuals with autism, was so low the use of correct only trials in the neuroimaging analyses greatly reduced the power to detect a signal. Indeed, previous research on an oddball task in individuals with autism found that the dlPFC was activated more to targets than to novels when all trials were considered, however this activation was no longer found in an analysis considering only trials in which a correct response was made (Shafritz et al., 2005). While it was not possible to disentangle whether the loss of activity in the dlPFC in this study was due to a true lack of dlPFC engagement when a correct response was made or due to a loss of power to detect the signal, it is an important cautionary tale for potential power loss when doing such analyses. Therefore, future studies need to focus on paradigms that have less of an accuracy cost. With respect to the current task, it was likely that much of the task difficulty was associated with the speed of stimulus presentation. The purpose of having such a quick design was to compensate for the

lack of eye-tracking capabilities and ensure that the stimuli were presented such that there was not enough time for the participants to saccade away from the eyes. Thus, future iterations of the current task should incorporate eye tracking technology to ensure that attention was being directed at the eyes and this would allow the stimulus presentation to be slowed. Slowed presentation would result in an increase in the time allocated for processing the stimulus, facilitating target detection and likely increasing accuracy on the task.

In addition to task and analysis related limitations, there are multiple concerns with respect to the composition of the high-functioning autism group. On the one hand, the group was comprised of only those individuals who were able to complete a difficult cognitive task. In addition, participants were required to be able to inhibit movement for as much as an hour and a half while the functional and structural MRI images were acquired. Thus, the current sample of individuals with high-functioning autism is not likely representative of the broader spectrum of individuals with autism, of which up to 51% suffer from intellectual disability (Centers for Disease Control, 2009). While the difficulty experienced by participants in the current version of the task suggests that this would not be a task that would be amenable to research on lower-functioning individuals, making some of the changes already highlighted may permit the use of this task in a less-functioning cohort of participants. Furthermore, the exclusion of individuals with any history of neurologic disorder or a family history of psychiatric disorder further decreased the representativeness of our sample. It is estimated that up to 30% of individuals with autism have a comorbid diagnosis of epilepsy and there is evidence for increased rates of major depression (33% of

parents) and social phobia (14% of parents) in family members of individuals with autism (Jeste, 2011; Piven and Palmer, 1999). While including these participants would have made it impossible to disambiguate findings that are specific to autism, it means that our results can only be extended to the subset of participants with autism fulfilling our stringent recruitment criteria. A final note is that, while all of the participants with autism in the current study were high-functioning there was still a significant amount of heterogeneity in the sample, which may have contributed to loss of power to detect differences. Thus, it is imperative that future research focuses on identifying endophenotypes that will permit researchers to target more homogeneous subgroups of participants.

An additional caveat is that all participants in the current study were over the age of 18. Thus, it was not possible to know whether differential findings in our participants with autism were associated with compensatory changes or whether they represent differences that were present early in development. Future research will need to employ similar paradigms to the one utilized in the present study in younger participants with autism. This will help to disambiguate which of the current findings are primary to the disorder and which much may represent compensatory changes. Insight into the primacy of the findings may help disambiguate current debate over the biological underpinnings of decreased eye contact in individuals with autism. The developmental significance of whether the decreased attention to eyes is due to increased cognitive demand associated with a lack of specialization in social neural networks, over-arousal in response to direct gaze, or a lack of motivation to attend to eyes has very different implications for early intervention.

In addition, a word of caution is warranted with respect to the use of functional connectivity analyses in studies of neurodevelopmental and neuropsychiatric disorders. A recent report highlighted the influence of task-independent effects on measures of task-associated functional connectivity. Specifically, this study cites neural fluctuations that were independent of the task-related brain activity as a primary source of functional connectivity findings in individuals with autism (Jones et al., 2010). While it is important to consider this concern, it is of note that this study employed only direct correlational techniques (e.g. creating a correlation matrix with which t-tests were performed on z-score transformed time-course information averaged from structurally defined ROIs) to explore functional connectivity in individuals with autism as compared to controls. While the current functional connectivity analysis technique also explores correlation between task-related time-course activity in a specific ROI and the rest of the brain, the current technique utilizes singular value decomposition, which is significantly more nuanced than a simple correlation analysis. Additionally, the current technique employed multiple methods to ensure that all results were statistically significant and reliably different from random noise. Specifically, the current protocol employed 500 iterations of permutation testing to the whole brain to determine the statistical significance of each latent variable. This was followed by 100 iterations of bootstrap testing to assess the stability of the task-related effects within each nonzero voxel (McIntosh et al., 2004). Thus, while it was not possible to fully rule out task-independent influences on the connectivity results, the multi-step correction process greatly reduces the chance that these non-task related signals account for current findings.

Furthermore, the current functional connectivity analysis only provides a snapshot of the neurofunctional differences between individuals with autism and neurotypical controls. Future studies need to investigate whether there is differential activation of networks in other regions important for integrating social and cognitive information, such as the amygdala. A seed-analysis on connections with the amygdala was conducted for both groups in the current study, however the resulting networks were not significant by permutation testing. It is possible that this lack of significant findings was due to the impact of the proximity of the amygdala to sinus cavities, which has been linked to a low signal-to-noise ratio and decreased signal detection (LaBar et al., 2001).

In addition, functional connectivity analyses do not provide any information about the underlying structural alterations that may be associated with the between group differences in functional networks. Thus, it will be important to investigate the role of structural alterations that may underlie the functional differences in the individuals with autism. Indeed, we are in the process of analyzing DTI data from the participants involved in the current study. This will allow us to investigate alterations in the morphology and diffusivity of the white matter tracts that connect the frontal executive, parietal attention, and social/emotional limbic regions, which may have contributed to group differences identified in the functional connectivity analyses.

The results from the current body of research leave open several unanswered questions. For example, while the difficulties with reciprocal social interactions are likely specific to autism spectrum disorders, how do the social cognitive deficits seen

in individuals with autism differ from those associated with other disorders, including schizophrenia? Our group has recently highlighted the importance of implementing studies in which there are comparisons across disorders (Sasson et al., in press). Elucidating how social deficits converge and diverge between disorders with different neurodevelopmental etiologies and trajectories will allow for a greater understanding of both biological underpinnings and developmental time course of these deficits. Furthermore, we did not address how the results from the current study may be associated with clinical severity in our participants with autism. Thus, it is unknown how the results from the current study may contribute to or be explained by the clinical heterogeneity within our cohort. Additionally, it is not possible to make assumptions about how our results contribute to the understanding of the clinical manifestation of autism without addressing how our findings are associated with clinical severity. Future research needs to focus on incorporating clinical batteries with functional and structural neuroimaging studies in order to better connect cognitive and neurobiological findings to clinical outcomes.

Finally, the understanding of the biological basis of the heterogeneity inherent in autism is still in its infancy. However, the clinical importance of understanding this heterogeneity is critical. Future research needs to move towards identifying neurobiological variables and characteristics that can impact intervention efficacy. Specifically, researchers need to work on integrating multiple neurobiological techniques with information about the efficacy of targeted behavioral and pharmacological interventions in individuals with autism. Taking this approach has the potential of allowing us to identify individuals who are predisposed to having

positive treatment outcomes. As such, the short-term impact of this type of research will be to elucidate how the heterogeneity in autism contributes to treatment outcome. Long-term, however taking this approach to autism research has the potential of allowing us to better streamline treatment plans and to move the field of autism intervention towards the “patient-centered” model that other medical disciplines (c.f. breast cancer treatment) have already embraced.

APPENDIX A. SUPPLEMENTARY TABLES

Main Cluster		BA	X	Y	Z	Max Z	Uncorrected p-value	Size
Target Eyes > (Target and Eyes)								
Occipital Fusiform Gyrus	R	18	30	-74	-6	3.68	0.0002	1027
Superior Parietal Lobule	L	40	-42	-36	53	3.39	0.0007	1727
Lateral Occipital Gyrus, superior division	L	19	-32	-73	18	3.10	0.0019	337
Occipital Fusiform Gyrus	L	18	-18	-76	-10	3.00	0.0027	619
Supplementary Motor Area	L	6	-6	-1	50	2.95	0.0032	322
Superior Parietal Lobule	R	7	36	-48	58	2.85	0.0044	159
Putamen	R	*	22	12	-2	2.78	0.0054	70
Cerebellum	R	*	10	-55	-11	2.74	0.0061	68
Intraparietal Sulcus, anterior division (hIP1)	R	7	28	-47	39	2.74	0.0061	64
Dorsolateral Prefrontal Cortex	L	9	-38	46	23	2.67	0.0076	29
Temporal Occipital Fusiform Gyrus (FFA)	L	37	-28	-46	-18	2.65	0.008	29
Precuneus	R	7	8	-68	46	2.62	0.0088	74
Superior Temporal Gyrus, posterior division	R	22	50	-35	4	2.59	0.0096	100
Superior Parietal Lobule	R	40	38	-36	57	2.50	0.0124	46
Angular Gyrus	R	40	50	-52	43	2.47	0.0135	32
Postcentral Gyrus	L	43	-61	-15	19	2.46	0.0139	50
Putamen	R	*	30	-8	2	2.45	0.0143	39
Middle Temporal Gyrus, posterior division	L	21	57	-28	-9	2.43	0.0151	56
Dorsolateral Prefrontal Cortex	R	9	42	13	25	2.41	0.016	46
Supramarginal Gyrus, posterior division	R	40	57	-41	30	2.40	0.0164	66
Precentral Gyrus	R	9	51	3	18	2.38	0.0173	86
Temporal Occipital Fusiform Gyrus (FFA)	L	37	-34	-45	-15	2.38	0.0173	22
Anterior Cingulate Cortex, dorsal	R	32	14	32	13	2.35	0.0188	38
Superior Temporal Gyrus, posterior division	L	22	-61	-31	3	2.34	0.0193	71

Table A.1. Foci of Activation from Uncorrected Contrast Analysis for Pure Social Target Condition in Neurotypical Participants.

Uncorrected analysis of regions activated more in the Target Eyes condition as compared to the conjunction of the Eyes Alone and the Target Alone condition. Regions were considered significant if they were comprised of at least 15 contiguous voxels and if they reached a Z-statistic threshold of $Z > 2.3$, which is equivalent to an uncorrected $p < 0.02$.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Angular Gyrus									
PGa	R	40	44	-52	52	2.8668	0.0041	29	1
Cerebellum									
Lobe I-IV	L	*	-4	-44	-28	3.4490	0.0006	24	1
Lobe V	R	*	8	-56	-20	3.3980	0.0007	20	2
Cingulate Cortex									
Anterior, dorsal	L	32	-4	32	28	3.1926	0.0014	28	6
	N/A	32	0	40	16	2.9009	0.0037	27	2
	R	32	12	16	28	3.3758	0.0007	26	3
	R	32	8	32	24	2.6012	0.0093	37	1
	R	32	16	36	28	2.5607	0.0104	24	7
Paracingulate	L	9	-12	40	28	2.6201	0.0088	26	7
	L	32	-4	12	44	3.1085	0.0019	85	4
Posterior	L	23	-8	-16	28	5.7391	0.0000	674	1
	R	24	16	-20	40	3.0167	0.0026	24	2
Frontal Cortex									
Dorsolateral Prefrontal Cortex	R	9	40	20	40	3.1446	0.0017	45	2
	R	9	48	24	28	3.0197	0.0025	17	1
	R	9	36	28	36	3.0080	0.0026	21	3
Orbital Frontal Cortex	R	47	16	20	-24	3.8764	0.0001	22	1
Ventrolateral Prefrontal Cortex	R	10	40	52	0	3.6970	0.0002	32	4
Ventromedial Prefrontal Cortex	R	10	12	68	-4	2.5685	0.0102	24	1
	R	11	24	48	-4	4.0778	0.0000	21	7
Fusiform Cortex									
Temporal, posterior division	L	20	-36	-16	-32	2.6196	0.0088	15	3
Intraparietal Sulcus									
Anterior division (hIP2)	L	40	-48	-40	40	3.0724	0.0021	21	2
Lingual Gyrus	L	19	-16	-56	-8	3.0035	0.0027	66	1
	R	19	28	-60	-4	3.4385	0.0006	16	1
Medial Globus Pallidius	L	*	-16	-8	-4	4.1144	0.0000	19	4
Opercular Cortex									
Central	L	13	-44	-20	20	3.6999	0.0002	33	2
Parahippocampal Gyrus									
Posterior division	L	35	-16	-36	-16	3.2582	0.0011	22	2
	R	35	16	-32	-16	3.5427	0.0004	97	1
Postcentral Gyrus	L	2	-48	-28	40	2.7714	0.0056	18	2
	R	2	40	-28	48	3.9259	0.0001	90	3
	R	3	40	-36	64	3.8757	0.0001	15	3
	R	4	44	-20	40	4.2255	0.0000	24	3
Precentral Gyrus	L	6	-20	-16	52	4.1676	0.0000	53	2
	L	31	-16	-24	40	3.1719	0.0015	18	3
	R	6	48	-4	44	3.1740	0.0015	16	2
	R	6	28	-8	60	2.8899	0.0039	17	4
	R	31	20	-36	44	4.5952	0.0000	215	4
Precuneus Cortex	L	30	-16	-56	8	2.6721	0.0075	17	1
Putamen, Lentiform Nucleus	R	*	24	12	-8	6.0638	0.0000	43	4
Superior Parietal Lobule	R	7	28	-52	56	2.7739	0.0055	17	7
Supplementary Motor Cortex	N/A	6	0	-4	56	3.0084	0.0026	32	2
Supramarginal Gyrus									
Anterior division	R	2	56	-28	36	3.2120	0.0013	35	6
Posterior division	L	40	-48	-40	32	3.9994	0.0001	151	3
	L	40	-52	-40	56	3.9713	0.0001	174	4
Temporal Cortex									
Middle, posterior division	R	*	52	-36	-4	3.7382	0.0002	24	1
Middle, anterior division	L	21	-52	-8	-20	2.9394	0.0033	23	1
Temporal Pole	R	38	36	4	-24	4.2752	0.0000	21	6

Table A.2. Foci of Activation from Positive Salience Network for Mean-Centering PLS in Neurotypical Controls.

Foci of Activation identifying regions differentially activated by the Target Alone condition as compared to the Eyes Alone and Target Eyes conditions BSR refers to the bootstrap ratio, which is approximately equivalent to a z-score and provides an estimation of how reliably each subject contributes to the significance of the LV. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Negative Salience									
Accumbens	R	*	12	20	-8	-4.2800	0.0000	103	4
Cingulate Cortex									
Anterior, dorsal	R	33	4	12	28	-3.1495	0.0016	39	6
Anterior, rostral	R	32	8	48	0	-4.2015	0.0000	344	6
Anterior, ventral	R	25	12	20	-12	-5.0544	0.0000	44	2
Posterior	L	29	-4	-48	12	-3.9321	0.0001	53	2
	L	30	-8	-52	20	-5.8695	0.0000	6184	5
	R	29	8	-44	12	-4.9103	0.0000	1916	4
Frontal Cortex									
Dorsolateral Prefrontal Cortex	R	9	40	8	24	-4.0181	0.0001	41	1
	R	9	20	44	24	-3.7390	0.0002	37	1
	R	10	28	44	20	-2.8435	0.0045	30	4
Dorsomedial Prefrontal Cortex	L	9	-20	36	24	-5.1503	0.0000	1133	1
	R	10	24	44	24	-4.0596	0.0000	31	2
	R	10	4	60	16	-2.9845	0.0028	17	1
Orbital Frontal Cortex	L	47	-16	8	-20	-4.8393	0.0000	58	2
	R	11	32	36	-16	-4.0520	0.0001	65	1
	R	11	16	28	-24	-3.7553	0.0002	22	5
	R	47	44	28	-8	-3.4051	0.0007	33	4
Superior Frontal Gyrus	L	6	-20	-8	68	-2.8785	0.0040	58	1
	L	8	-20	28	40	-3.8979	0.0001	19	7
	L	8	-20	40	40	-2.5784	0.0099	32	7
	R	6	4	12	68	-3.3445	0.0008	35	6
Ventrolateral Prefrontal Cortex	L	11	-28	48	-8	-3.5999	0.0003	38	2
	L	44	-48	20	4	-2.7112	0.0067	16	4
	R	13	36	24	16	-5.4756	0.0000	128	5
	R	13	40	20	20	-5.0051	0.0000	148	3
	R	45	48	24	12	-5.1216	0.0000	630	2
	R	45	48	36	8	-3.0373	0.0024	46	7
Ventromedial Prefrontal Cortex	L	10	-24	64	-4	-3.5215	0.0004	35	1
	L	11	-16	60	-12	-3.3932	0.0007	16	2
Fusiform Cortex									
Temporal Occipital (FFA)	L	37	-40	-52	-12	-3.0692	0.0021	78	4
	R	37	24	-48	-16	-3.0853	0.0020	25	1
Occipital Cortex									
Lateral, inferior divison	R	18	28	-80	0	-5.1420	0.0000	278	1
Lateral, superior divison	L	7	-12	-80	44	-6.7443	0.0000	5070	6
	L	19	-36	-88	20	-3.0249	0.0025	31	1
	L	39	-40	-72	36	-2.9801	0.0029	16	2
	R	19	32	-76	16	-5.6604	0.0000	1222	2
Occipital Pole	L	18	-12	-104	12	-3.0059	0.0026	32	1
Opercular Cortex									
Central	R	*	52	4	0	-2.6427	0.0082	69	4
Frontal	L	45	-44	20	4	-4.6470	0.0000	219	1
	R	13	40	16	8	-5.1258	0.0000	372	1
Parietal	L	13	-36	-40	24	-11.0489	0.0000	5110	7
Postcentral Gyrus	L	5	-4	-48	76	-5.4649	0.0000	3141	3
	R	2	24	-40	68	-3.5485	0.0004	40	2
	R	3	12	-36	64	-3.5727	0.0004	40	3
Precentral Gyrus	L	4	-32	-16	52	-2.9562	0.0031	43	4
	L	6	-48	-4	44	-4.6808	0.0000	45	4
	L	6	-4	-24	68	-3.5622	0.0004	79	3
	L	31	-8	-16	48	-5.4797	0.0000	865	2
	R	6	40	-12	44	-2.8997	0.0037	16	7
Precuneus Cortex	R	7	16	-48	40	-2.7470	0.0060	27	2
Putamen	L	*	-32	-8	4	-4.0290	0.0001	160	1
	R	*	16	-16	-8	-3.5852	0.0003	41	4
Superior Parietal Lobule	L	7	-20	-56	68	-5.2400	0.0000	96	1
Supplementary Motor Cortex	R	6	4	-12	64	-4.7887	0.0000	151	4
Supracalcarine Cortex	L	30	-20	-68	16	-4.3863	0.0000	171	1
Temporal Cortex									
Middle, anterior division	L	21	-48	-4	-24	-4.2371	0.0000	292	4
Middle, posterior division	L	21	-56	-24	-12	-2.5553	0.0106	16	1
	L	22	-48	-44	0	-5.2142	0.0000	492	2
Middle, temporooccipital part	R	22	48	-48	8	-3.6507	0.0003	63	1
	R	37	52	-52	-4	-3.1598	0.0016	23	7
Planum Polare	R	22	60	4	0	-3.1211	0.0018	19	3
Planum Temporale	L	42	-56	-32	12	-2.5551	0.0106	19	3
Temporal Pole	L	22	-48	8	-8	-2.9972	0.0027	21	1
Thalamus	L	*	-12	-24	-4	-2.7477	0.0060	29	4

Table A.3. Foci of Activation from Negative Salience Network for Mean-Centering PLS in Neurotypical Controls.

Foci of Activation identifying regions differentially activated by the Eyes Alone and Target Eyes conditions as compared to the Target Alone condition. BSR refers to the bootstrap ratio, which is approximately equivalent to a z-score and provides an estimation of how reliably each subject contributes to the significance of the LV. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Seed	TD FSL			HFA FSL			TD PLS			Group PLS		
	x	y	z	x	y	z	x	y	z	x	y	z
Right Orbital Frontal Cortex (BA 47)	34	28	-6	42	22	-10	44	28	-8	48	24	-12
Right Dorsolateral Prefrontal Cortex (BA 9/46)	48	10	22	46	24	30	40	8	24	40	16	24
Left Ventrolateral Prefrontal Cortex (BA 44)	-50	12	0	-	-	-	-48	20	4	-	-	-

Table A.4. Regions Identified for Seed PLS Analyses

MNI coordinates of regions used for functional connectivity analyses. Regions were picked in the neurotypical (TD) group based on overlap between region-based FSL analysis on the Target Eyes condition and the mean-centering PLS analysis. Regions for the individuals with high-functioning autism (HFA) were picked based on similarity to regions utilized in the TD seed-PLS analysis, however it is of note that similar regions were found in the HFA FSL analysis.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Accumbens	R	*	8	16	-4	5.8092	0.0000	34	7
Amygdala	L	*	-20	0	-12	5.9076	0.0000	34	4
Angular Gyrus									
PGa	R	22	64	-56	16	5.4608	0.0000	28	5
Caudate Body	R	*	16	12	8	8.4563	0.0000	45	3
Cerebellum									
Lobule V	R	*	16	-48	-24	5.2077	0.0000	16	5
Cingulate Cortex									
Anterior, dorsal	L	24	-4	-12	44	4.2857	0.0000	18	4
	R	32	8	4	44	8.1947	0.0000	116	2
	R	32	8	16	36	6.7927	0.0000	28	1
Anterior, rostral	N/A	32	0	44	12	4.9559	0.0000	16	6
Anterior, ventral	L	32	-4	40	-4	5.2815	0.0000	21	4
	R	24	4	36	-8	6.0076	0.0000	22	7
	R	25	12	24	-8	5.7363	0.0000	76	5
Paracingulate	R	32	12	12	40	8.1408	0.0000	197	3
Posterior	R	31	8	-24	44	9.0881	0.0000	422	5
	R	31	8	-48	36	8.2622	0.0000	71	3
Frontal Cortex									
Dorsolateral Prefrontal Cortex	L	46	-44	24	20	5.7116	0.0000	17	5
Dorsomedial Prefrontal Cortex	L	10	-24	52	16	5.9812	0.0000	15	4
Orbital Frontal Cortex	L	47	-44	28	-12	4.7194	0.0000	22	6
Ventrolateral Prefrontal Cortex	L	11	-28	36	-20	5.1223	0.0000	27	7
	R	47	52	24	0	5.4406	0.0000	23	3
Ventromedial Prefrontal Cortex	R	11	24	44	-4	5.5532	0.0000	16	3
	R	32	4	36	-12	5.0952	0.0000	46	6
Heschl's Gyrus	R	6	52	-8	4	7.6463	0.0000	134	5
Hippocampus	R	27	24	-32	-8	5.8682	0.0000	15	6
Insular Cortex	L	*	-32	20	0	6.1686	0.0000	18	6
Intracalcarine Cortex	R	18	12	-72	12	5.9120	0.0000	36	6
	R	30	20	-64	4	6.6343	0.0000	53	5
Intraparietal Sulcus									
Anterior division (hIP1)	R	40	36	-48	32	4.9200	0.0000	16	3
Lingual Gyrus	L	19	-12	-52	0	7.2691	0.0000	16	4
	L	*	-20	-48	0	4.8783	0.0000	21	6
	R	19	12	-60	0	4.8851	0.0000	16	3
Occipital Cortex									
Lateral, superior division	L	19	-24	-88	24	5.0901	0.0000	23	3
	L	19	-28	-84	40	6.2126	0.0000	15	5
	R	19	36	-76	16	4.9910	0.0000	26	3
	R	39	52	-60	20	6.2253	0.0000	35	3
Opercular Cortex									
Central	L	13	-44	-16	20	5.0091	0.0000	32	6
	L	43	-52	-8	8	5.7577	0.0000	63	3
	R	6	52	-4	4	6.4735	0.0000	55	3
Parietal	R	13	48	-28	24	5.0118	0.0000	19	3
	R	40	52	-32	24	6.6104	0.0000	28	4
	R	40	52	-28	20	5.4578	0.0000	21	5
Postcentral Gyrus	L	3	-24	-36	56	5.2165	0.0000	16	3
	L	5	-16	-36	48	7.9697	0.0000	374	6
	L	5	-12	-36	52	7.2624	0.0000	47	7
Precentral Gyrus	L	6	-52	-4	36	4.9790	0.0000	16	2
	L	6	-60	0	20	4.9236	0.0000	16	2
	L	43	-60	-4	12	5.9528	0.0000	80	4
	L	*	-16	-24	44	5.5628	0.0000	21	7
	R	6	32	-4	52	8.3046	0.0000	17	5
Precuneus Cortex	L	29	-12	-52	4	8.8178	0.0000	61	5
	R	7	8	-56	40	5.8215	0.0000	28	4
	R	7	8	-56	40	5.8432	0.0000	30	5
	R	7	12	-64	36	5.2783	0.0000	15	6
	R	23	8	-60	16	5.1756	0.0000	55	5
	R	31	12	-56	20	5.0956	0.0000	20	4
Putamen	L	*	-28	0	-4	5.7600	0.0000	31	3
	L	*	-28	8	0	5.9876	0.0000	27	5
Supplementary Motor Cortex	R	6	8	-12	52	6.5773	0.0000	102	4
	R	6	4	-8	68	7.2893	0.0000	172	7
Temporal Cortex									
Planum Polare	L	22	-52	4	-4	7.8761	0.0000	169	5
	L	22	-52	4	-4	6.6327	0.0000	49	6
	L	22	-56	-4	0	6.9274	0.0000	29	7
	R	21	44	-8	-16	6.7282	0.0000	88	6
	R	22	56	-4	0	6.3595	0.0000	155	4
Planum Temporale	L	42	-56	-32	12	5.1567	0.0000	17	3
	R	41	52	-32	12	5.0358	0.0000	20	2
	R	41	36	-32	12	5.4784	0.0000	27	6
Temporal Pole	R	38	52	16	-8	6.8642	0.0000	18	7
Thalamus									
Medial Dorsal Nucleus	R	*	16	-28	-4	6.4108	0.0000	30	4
Pulvinar Nucleus	R		16	-32	4	4.9126	0.0000	21	3

Table A.5. Foci of Activation from Seed-PLS Analysis of Neural Networks Functionally Connected to the Right OFC in Neurotypical Controls.

Regions comprising the functional network associated with the right OFC and its interactions with task performance (RT). Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Angular Gyrus									
PGa	L	22	-52	-56	16	4.5573	0.0000	28	1
Cingulate Cortex									
Anterior, dorsal	L	9	-12	44	20	3.1226	0.0018	19	6
	L	24	-4	12	32	4.5791	0.0000	16	6
	L	24	-12	8	32	3.9790	0.0001	21	7
	R	24	12	8	36	5.0740	0.0000	128	6
	R	24	12	4	36	3.4058	0.0007	22	5
Anterior, rostral	L	32	-8	40	12	3.3856	0.0007	21	1
	N/A	32	0	36	-4	4.7262	0.0000	49	2
Anterior, ventral	R	32	8	36	-8	6.6870	0.0000	77	1
Posterior	L	31	-12	-28	36	5.0949	0.0000	18	1
	N/A	31	0	-28	40	4.9741	0.0000	31	7
	R	23	8	-48	24	3.6790	0.0002	19	6
Caudate Body	L	*	-20	16	12	3.4598	0.0005	23	1
Frontal Cortex									
Dorsolateral Prefrontal Cortex	L	9	-36	20	40	5.6541	0.0000	112	7
Dorsomedial Prefrontal Cortex	N/A	10	0	68	8	6.2260	0.0000	18	5
	R	9	16	40	44	4.7758	0.0000	16	2
	R	9	16	40	40	4.3600	0.0000	24	4
	R	10	8	64	24	5.1991	0.0000	629	7
Middle Frontal Gyrus	L	*	-32	28	28	5.1374	0.0000	28	6
Orbital Frontal Cortex	R	11	24	32	-20	6.4398	0.0000	18	1
	R	38	28	12	-24	3.8158	0.0001	15	7
Superior Frontal Gyrus	R	6	20	-12	56	6.1959	0.0000	44	7
	R	8	4	36	48	4.7041	0.0000	56	5
	R	32	20	16	40	4.1581	0.0000	22	2
Ventrolateral Prefrontal Cortex	L	45	-52	32	4	4.2732	0.0000	33	1
	L	45	-44	20	16	4.2366	0.0000	49	7
Ventromedial Prefrontal Cortex	L	10	-4	56	-4	3.5587	0.0004	15	2
	L	11	-4	32	-20	4.9674	0.0000	21	5
	R	10	32	56	12	4.1263	0.0000	18	2
Fusiform Cortex									
Occipital	L	18	-32	-80	-8	3.8965	0.0001	20	4
	L	19	-24	-76	-4	4.2196	0.0000	15	5
Temporal, posterior division	L	20	-40	-32	-20	4.3774	0.0000	23	6
Heschl's Gyrus	L	41	-48	-24	12	5.1912	0.0000	32	1
Hippocampus	R	*	32	-16	-20	3.8257	0.0001	19	6
Insular Cortex	L	*	-32	-4	12	5.1150	0.0000	86	1
Intraparietal Sulcus									
Posterior division (hIP3)	L	7	-16	-56	40	4.2503	0.0000	34	7
Lingual Gyrus	L	*	-20	-48	0	6.0919	0.0000	33	7
	R	19	16	-64	-4	5.9175	0.0000	31	2
	R	19	28	-56	-4	5.3690	0.0000	23	6
Occipital Cortex									
Lateral, inferior division	L	18	-28	-84	-4	4.0763	0.0000	26	7
	R	19	40	-76	-4	3.4358	0.0006	22	7
	R	37	60	-68	8	5.6065	0.0000	36	2
Lateral, superior division	L	39	-48	-64	28	5.3397	0.0000	53	2
	L	39	-48	-76	28	3.8129	0.0001	28	7
	L	40	-48	-60	48	5.6103	0.0000	68	7
	R	7	20	-68	48	5.1210	0.0000	41	1
	R	7	24	-64	60	3.9407	0.0001	20	2
	R	39	52	-72	4	5.7733	0.0000	99	1

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Opercular Cortex									
Central	L	22	-52	0	4	3.2001	0.0014	15	7
	R	13	36	-16	20	4.7246	0.0000	32	2
Parahippocampal Gyrus									
Posterior division	R	35	20	-24	-16	4.2676	0.0000	46	7
Postcentral Gyrus	L	1	-52	-20	52	4.2123	0.0000	22	2
	R	2	40	-24	44	4.0115	0.0001	16	1
Precentral Gyrus	L	4	-52	-8	44	5.0877	0.0000	24	1
	L	4	-24	-24	64	4.1029	0.0000	17	7
	L	6	-4	-20	64	5.5677	0.0000	40	7
	L	6	-28	-12	48	4.9701	0.0000	24	1
	L	6	-28	-16	48	4.7129	0.0000	19	7
	L	6	-16	-12	76	4.0984	0.0000	16	6
	L	6	-16	-16	68	4.0051	0.0001	19	2
	L	6	-60	0	8	3.6844	0.0002	36	6
	L	9	-56	8	32	4.0130	0.0001	17	5
	L	44	-56	8	24	4.9731	0.0000	19	4
Precuneus Cortex									
	L	7	-8	-60	44	3.5042	0.0005	17	1
	L	18	-28	-60	4	4.8022	0.0000	66	1
	R	30	8	-52	12	3.3804	0.0007	17	7
	R	31	16	-60	32	3.7633	0.0002	52	7
Superior Parietal Lobule	R	3	28	-40	52	4.3862	0.0000	15	1
Supramarginal Gyrus									
Anterior division	L	40	-64	-40	36	3.5743	0.0004	22	1
Posterior division	L	13	-56	-48	16	5.3702	0.0000	33	2
	L	22	-68	-48	12	5.1473	0.0000	31	7
	L	40	-56	-48	24	6.0144	0.0000	29	6
	L	40	-32	-44	36	4.2921	0.0000	33	7
	L	40	-56	-44	48	3.3136	0.0009	16	2
	R	21	60	-20	-4	6.8864	0.0000	125	2
Temporal Cortex									
Inferior, temporooccipital part	L	37	-52	-56	-16	4.4351	0.0000	21	6
Middle, anterior division	L	20	-48	-8	-24	5.3859	0.0000	21	5
Middle, posterior division	L	21	-56	-24	-16	5.2218	0.0000	17	2
	L	21	-64	-36	-8	4.9962	0.0000	20	5
Planum Polare	L	22	-48	-4	-4	4.5372	0.0000	17	1
	L	*	-52	-4	0	3.8204	0.0001	28	2
	R	22	56	-4	0	4.2246	0.0000	34	3
Planum Temporale	L	13	-40	-44	12	4.6051	0.0000	21	2
Superior, anterior division	L	20	-44	-4	-24	4.5763	0.0000	36	3
	L	21	-56	-4	-12	3.5649	0.0004	17	6
	R	21	52	0	-20	4.5302	0.0000	15	7
	R	38	52	4	-20	5.3839	0.0000	34	2
Superior, posterior division	R	13	48	-16	-4	5.8379	0.0000	226	1

Table A.6. Foci of Activation from Positive Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Left vlPFC in Neurotypical Controls.

Regions comprising the functional network associated with activity in the left vlPFC and its interactions with task performance (RT). Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Negative Salience									
Caudate Body	L	*	-8	4	12	-4.1237	0.0000	22	3
Cerebellum									
Lobule I-IV	R	*	4	-44	-16	-5.0023	0.0000	23	4
Lobule V	R	19	16	-56	-12	-4.0858	0.0000	21	4
Lobule VI	R	19	24	-56	-20	-4.7873	0.0000	43	5
Vermis VI	L	*	-4	-68	-16	-3.5436	0.0004	17	4
Cingulate Cortex									
Posterior	N/A	23	0	-36	20	-3.6061	0.0003	28	4
Cuneal Cortex	L	18	-4	-72	20	-3.9863	0.0001	48	5
	L	18	-8	-76	28	-3.8787	0.0001	16	7
	L	31	-12	-76	28	-3.3090	0.0009	17	6
	R	7	4	-76	36	-3.7465	0.0002	17	1
	R	18	16	-72	20	-3.7255	0.0002	32	6
	R	19	12	-84	36	-4.7881	0.0000	41	7
	R	19	4	-84	28	-3.4326	0.0006	23	3
Frontal Cortex									
Dorsolateral Prefrontal Cortex	R	46	44	36	16	-4.2780	0.0000	16	7
Middle Frontal Gyrus	L	6	-28	12	56	-3.6992	0.0002	25	3
	L	8	-48	16	44	-4.0442	0.0001	22	6
	L	8	-52	8	44	-3.7738	0.0002	15	7
Orbital Frontal Cortex	L	47	-40	24	-8	-6.2794	0.0000	114	4
	L	47	-40	20	-8	-5.8054	0.0000	25	5
	L	47	-32	36	4	-4.9232	0.0000	27	4
	L	47	-40	20	-16	-4.4570	0.0000	17	1
	R	47	40	32	0	-10.0414	0.0000	881	5
	R	47	16	28	-20	-3.9442	0.0001	17	5
Superior Frontal Gyrus	L	6	-4	32	56	-4.4855	0.0000	17	4
	L	24	-20	4	44	-3.7134	0.0002	31	5
	L	32	-8	20	48	-3.5090	0.0004	18	5
Ventrolateral Prefrontal Cortex	L	10	-40	48	0	-5.8833	0.0000	628	5
	L	46	-52	32	12	-5.5620	0.0000	28	7
	R	10	40	40	0	-5.1163	0.0000	23	7
Insular Cortex	L	47	-36	16	-8	-4.1691	0.0000	47	3
	L	*	-32	12	0	-4.1827	0.0000	36	2
	L	*	-36	-12	-8	-6.7658	0.0000	24	6
	R	*	32	12	-4	-5.7891	0.0000	92	6
Intraparietal Sulcus									
Anterior division (hIP1)	L	39	-40	-52	24	-5.3253	0.0000	17	6
Lateral Globus Pallidus	L	*	-24	-12	-8	-4.1553	0.0000	21	3
Lingual Gyrus	L	30	-28	-56	0	-4.2521	0.0000	29	5
Occipital Cortex									
Lateral, inferior division	R	19	36	-68	8	-4.7512	0.0000	20	5
Lateral, superior division	L	7	-24	-60	60	-4.0457	0.0001	26	5
Occipital Pole	R	19	4	-92	28	-5.5657	0.0000	136	5
Opercular Cortex									
Central	L	13	-40	-12	24	-6.6716	0.0000	527	4
	L	13	-36	8	8	-3.8088	0.0001	18	6
	L	*	-36	-20	28	-3.1387	0.0017	15	2
	R	13	36	8	16	-6.5785	0.0000	172	3
Frontal	R	13	40	12	8	-4.0834	0.0000	34	7
Parietal	R	13	48	-36	24	-6.4401	0.0000	202	5
Postcentral Gyrus	L	3	-40	-28	52	-4.7530	0.0000	75	5
Precentral Gyrus	L	4	-40	-12	60	-3.4941	0.0005	16	3
	L	6	-40	4	36	-4.7087	0.0000	24	3
	L	6	-48	4	40	-3.4893	0.0005	31	5
	L	6	-8	-12	72	-3.2613	0.0011	20	4
	R	4	16	-28	56	-3.5740	0.0004	39	4
	R	6	48	0	32	-3.8492	0.0001	15	6
	R	6	12	-28	56	-3.5616	0.0004	19	5
	R	6	36	-12	44	-3.2480	0.0012	20	5
Precuneus Cortex	N/A	7	0	-76	56	-4.5129	0.0000	21	3
	R	7	8	-72	40	-4.7076	0.0000	106	4
	R	7	4	-72	64	-3.9512	0.0001	55	5
	R	7	4	-56	60	-3.3998	0.0007	22	6
Putamen	L	*	-32	-12	-4	-5.4687	0.0000	93	7
	R	*	32	-16	0	-6.6631	0.0000	15	6
	R	*	28	-20	0	-4.7061	0.0000	38	7
Supplementary Motor Cortex	L	6	-8	0	64	-7.4054	0.0000	103	3
	N/A	6	0	0	64	-5.3835	0.0000	59	5
	R	6	4	0	60	-5.1384	0.0000	98	4
Supramarginal Gyrus									
Anterior division	L	40	-64	-28	28	-5.1296	0.0000	21	6
Posterior division	R	13	60	-40	20	-3.2180	0.0013	15	7
	R	40	52	-40	28	-4.6999	0.0000	52	4
	R	40	52	-40	48	-4.3222	0.0000	39	6
Thalamus									
	N/A	*	0	-24	4	-5.3024	0.0000	50	6
Pulvinar Nucleus	R	*	20	-28	12	-4.9232	0.0000	24	7
Temporal Cortex									
Middle, posterior division	L	22	-48	-40	-4	-6.1250	0.0000	19	5
Planum Polare	L	22	-44	0	-4	-5.1110	0.0000	83	6
Planum Temporale	L	42	-60	-36	16	-3.7639	0.0002	18	3

Table A.7. Foci of Activation from Negative Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Left vlPFC in Neurotypical Controls.

Regions comprising the functional network associated with activity in the left vlPFC and its interactions with task performance (RT). Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Amygdala	R	*	32	0	-28	5.4858	0.0000	34	3
Caudate Body	R	*	16	-8	20	4.3672	0.0000	25	1
Cerebellum									
Lobule I-IV	R	30	12	-40	-16	4.6177	0.0000	112	3
	R	*	12	-36	-20	3.1361	0.0017	20	4
Lobule V	L	*	-24	-32	-32	5.7382	0.0000	41	2
	L	*	-24	-40	-32	3.7473	0.0002	29	7
	R	20	28	-40	-24	4.4242	0.0000	42	3
Cingulate Cortex									
Anterior, dorsal	L	32	-4	32	20	3.7533	0.0002	73	3
Anterior, ventral	R	11	8	20	-24	5.7491	0.0000	30	7
	R	11	8	16	-24	5.5773	0.0000	16	4
	R	11	8	20	-20	4.0332	0.0001	24	3
Posterior	L	23	-4	-40	24	3.9811	0.0001	139	1
	L	29	-4	-44	12	4.6204	0.0000	149	1
	N/A	23	0	-44	24	5.6893	0.0000	479	2
	R	31	12	-40	32	3.3165	0.0009	43	3
Cuneal Cortex	L	17	-20	-76	16	3.5777	0.0003	15	1
Frontal Cortex									
Dorsomedial Prefrontal Cortex	L	10	-12	72	8	3.2495	0.0012	42	7
	N/A	10	0	64	20	4.4589	0.0000	78	6
Frontal Pole	L	8	-12	56	36	2.9358	0.0033	23	2
Orbital Frontal Cortex	L	11	-36	36	-16	5.6355	0.0000	19	2
	R	45	28	28	8	4.4929	0.0000	308	7
	R	47	28	28	-20	2.9283	0.0034	20	1
Superior Frontal Gyrus	L	8	-4	36	48	4.1558	0.0000	20	7
Ventrolateral Prefrontal Cortex	L	44	-48	8	24	3.0562	0.0022	16	1
	L	45	-56	12	24	3.9169	0.0001	17	3
	L	45	-56	12	24	3.0930	0.0020	27	5
	L	46	-56	32	16	3.0827	0.0021	15	4
Ventromedial Prefrontal Cortex	N/A	10	0	52	-8	4.4904	0.0000	54	3
	N/A	11	0	56	-12	5.8516	0.0000	214	2
	R	10	4	56	-4	3.4840	0.0005	30	4
	R	11	4	40	-16	3.8638	0.0001	72	1
	R	*	32	40	4	5.7445	0.0000	62	1
	R	*	32	40	4	3.5414	0.0004	40	2
Fusiform Cortex									
Temporal, posterior division	L	36	-28	-32	-28	3.4525	0.0006	75	4
Temporal Occipital (FFA)	L	37	-36	-60	-12	3.9217	0.0001	62	2
Hippocampus	L	28	-16	-16	-16	3.6481	0.0003	16	7
	L	28	-12	-12	-16	3.5002	0.0005	21	2
	R	35	24	-24	-16	3.1237	0.0018	47	1
Intraparietal Sulcus									
Posterior division (hIP3)	R	7	36	-64	48	3.5569	0.0004	15	3
Lingual Gyrus	R	18	8	-56	0	3.2031	0.0014	24	1
Occipital Cortex									
Lateral, inferior division	R	19	40	-80	-8	3.3144	0.0009	24	2
Lateral, superior division	L	7	-24	-60	68	5.3997	0.0000	16	2
	L	7	-44	-68	44	4.2029	0.0000	54	2
	L	39	-44	-68	24	2.9591	0.0031	58	1
	R	7	16	-72	60	4.9259	0.0000	27	1
	R	18	20	-92	8	4.1376	0.0000	22	1
	R	39	52	-64	40	3.7635	0.0002	28	2
	R	39	32	-72	28	3.5141	0.0004	28	1
	R	39	52	-76	16	3.4631	0.0005	43	2
Occipital Pole	R	39	52	-68	32	3.2548	0.0011	25	1
Parahippocampal Gyrus									
Posterior division	R	36	24	-32	-16	4.6880	0.0000	149	2
	R	36	24	-32	-20	3.1266	0.0018	16	6
Precentral Gyrus	L	6	-56	4	28	4.3413	0.0000	120	7
	L	9	-52	4	28	3.9281	0.0001	38	6
	R	4	24	-24	48	5.2405	0.0000	20	2
Precuneus Cortex	L	7	-4	-72	40	3.9755	0.0001	41	1
	R	5	12	-40	48	4.3913	0.0000	114	1
	R	30	24	-48	8	3.6417	0.0003	66	2
	R	31	12	-52	24	3.4823	0.0005	30	2
Superior Parietal Lobule	R	*	28	-44	48	3.5779	0.0003	15	2
Temporal Cortex									
Inferior, anterior division	L	20	-44	-8	-28	2.9719	0.0030	22	1
	L	20	-52	-12	-28	3.0290	0.0025	16	3
Temporal Cortex									
Inferior, posterior division	L	37	-48	-36	-12	2.9357	0.0033	20	1
Inferior, temporooccipital part	R	37	48	-44	-8	3.3573	0.0008	57	2
Middle, posterior division	L	21	-56	-20	-20	2.9379	0.0033	41	2
	R	21	64	-16	-12	3.0798	0.0021	35	1
Planum Temporale	L	13	-32	-32	12	2.9586	0.0031	19	1
Superior, anterior division	L	21	-48	-8	-12	3.6370	0.0003	70	1
	L	21	-52	-8	-12	4.1890	0.0000	38	2
	R	21	56	0	-8	5.7289	0.0000	79	1
	R	21	48	-4	-20	4.7207	0.0000	161	2
	R	22	60	4	-4	3.7330	0.0002	40	2
Temporal Pole	R	13	44	8	-12	3.3871	0.0007	20	1

Table A.8. Foci of Activation from Positive Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Right dlPFC in Neurotypical Controls.

Regions comprising the functional network associated with activity in the right dlPFC and its influence on RT. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Negative Salience									
Caudate Body	L	*	-20	12	16	-13.7915	0.0000	9145	4
Cerebellum									
Lobule I-IV	N/A	*	0	-48	-8	-5.9585	0.0000	22	3
Lobule V	L	*	-4	-56	-20	-4.3008	0.0000	67	3
Lobule VI	R	*	28	-56	-24	-3.2980	0.0010	35	3
Cingulate Cortex									
Anterior, rostral	R	10	16	52	8	-3.9245	0.0001	84	2
Anterior, ventral	R	10	12	56	-4	-5.2128	0.0000	17	7
	R	10	12	48	4	-3.2046	0.0014	53	3
	R	25	4	8	-16	-4.3181	0.0000	15	7
	R	*	12	16	-12	-5.2801	0.0000	23	1
Frontal Cortex									
Doroslateral Prefrontal Cortex	L	9	-52	8	40	-8.9532	0.0000	3777	1
Dorsomedial Prefrontal Cortex	R	10	24	52	16	-3.8342	0.0001	24	7
Orbital Frontal Cortex	L	47	-32	32	-20	-8.8208	0.0000	6948	7
	R	47	36	28	-20	-4.5431	0.0000	22	2
Ventromedial Prefrontal Cortex	R	10	8	56	-8	-5.1782	0.0000	32	1
	R	10	20	56	-8	-3.5042	0.0005	21	1
	R	11	8	48	-16	-5.8323	0.0000	58	7
Insular Cortex	L	*	-32	-24	4	-3.9706	0.0001	19	2
Intracalcarine Cortex	L	30	-12	-68	8	-9.1589	0.0000	12456	5
Intraparietal Sulcus									
Anterior division (hIP2)	R	40	48	-36	36	-3.9053	0.0001	44	1
Posterior division (hIP3)	L	7	-16	-56	44	-3.7364	0.0002	48	1
Lingual Gyrus	L	19	-32	-44	-4	-4.6095	0.0000	32	2
	R	18	20	-76	0	-3.4443	0.0006	39	1
	R	30	24	-56	0	-3.1197	0.0018	23	3
Occipital Cortex									
Lateral, inferior division	L	19	-36	-68	12	-5.8494	0.0000	137	2
	R	19	40	-60	12	-3.5167	0.0004	78	2
Lateral, superior division	L	7	-36	-68	44	-5.6237	0.0000	16	1
	R	39	40	-68	16	-6.9198	0.0000	82	1
Occipital Pole	L	19	-24	-92	12	-6.9750	0.0000	236	1
	L	19	-20	-92	28	-3.4875	0.0005	25	2
	R	18	8	-96	16	-5.8285	0.0000	60	1
	R	18	4	-96	16	-4.5204	0.0000	60	2
	R	18	12	-100	4	-3.3746	0.0007	15	3
Operculum Cortex									
Pareital	L	13	-44	-36	24	-8.2098	0.0000	235	7
	R	13	52	-20	20	-3.7194	0.0002	53	1
Postcentral Gyrus	L	5	-12	-40	56	-3.6556	0.0003	56	2
	R	3	16	-40	64	-3.5254	0.0004	51	2
Precentral Gyrus	L	6	-52	0	44	-8.3416	0.0000	6949	3
Precuneus Cortex	L	7	-12	-72	36	-4.4729	0.0000	42	2
Putamen	L	*	-24	4	-8	-6.3267	0.0000	2777	2
Superior Parietal Lobule	L	7	-28	-44	64	-3.1110	0.0019	25	2
	R	7	20	-52	68	-3.1169	0.0018	17	2
Supramarginal Gyrus									
Posterior Division	R	40	56	-44	28	-4.1734	0.0000	71	2
Temporal Cortex									
Inferior, posterior division	R	20	44	-32	-16	-5.5367	0.0000	32	1
Middle, temporooccipital part	R	37	56	-52	-4	-3.0696	0.0021	15	7
Planum Polare	R	13	40	-28	4	-3.4938	0.0005	31	2
Superior, posterior division	L	22	-64	-36	8	-3.3771	0.0007	19	2
Thalamus	R	*	24	-24	16	-9.4473	0.0000	10316	6

Table A.9. Foci of Activation from Negative Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Right dlPFC in Neurotypical Controls.

Regions comprising the functional network associated with activity in the right dlPFC and its influence on RT. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Main Cluster		BA	X	Y	Z	Max Z	Uncorrected p-value	Size
Target Eyes > (Target and Eyes)								
Postcentral Gyrus	L	3	-38	-28	52	3.01	0.0026	421
Lateral Occipital Cortex, inferior division	L	19	-42	-72	-10	2.93	0.0034	55
Cerebellum, V	R	*	18	-52	-28	2.92	0.0035	32
Occipital Pole	R	17	18	-94	-4	2.90	0.0037	14
Insular Cortex	R	47	36	20	-2	2.89	0.0039	16
Precentral Gyrus	R	6	32	0	34	2.85	0.0044	69
Lingual Gyrus	L	18	-4	-80	0	2.82	0.0048	21
Occipital Fusiform Gyrus	R	18	28	-72	-16	2.81	0.005	15
Occipital Fusiform Gyrus	R	18	22	-80	-12	2.73	0.0063	24
Anterior Cingulate Gyrus, dorsal	N/A	24	0	20	30	2.72	0.0065	15
Occipital Fusiform Gyrus	L	18	-28	-80	-14	2.71	0.0067	41
Supplementary Motor Cortex	N/A	6	0	4	50	2.69	0.0071	24
Intraparietal Sulcus, anterior division (hIP1)	R	40	38	-52	46	2.61	0.0091	45
Postcentral Gyrus	R	6	48	-16	26	2.60	0.0093	13
Heschl's Gyrus	L	4	-54	-16	28	2.58	0.0099	14

Table A.10. Foci of Activation from Uncorrected Contrast Analysis for Pure Social Target Condition in Individuals with Autism

The Pure Social Target condition contrast represents an uncorrected analysis in which regions were considered significant if they comprised 15 contiguous voxels that reached a Z-statistic threshold of $Z > 2.3$, which is equivalent to an uncorrected $p < 0.02$.

Region	BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience								
Amygdala	* L	-20	0	-24	2.43	0.0152	15	6
Caudate	* L	-16	12	8	2.30	0.0214	26	5
	* R	16	24	-4	3.11	0.0019	85	1
Cerebellum	* L	-12	-40	-24	3.20	0.0014	15	3
Lobule I-IV								
Cingulate Gyrus								
Anterior , rostral	24 R	8	32	4	4.44	0.0000	41	5
	32 R	12	40	0	2.38	0.0171	28	2
Anterior, ventral	11 L	-8	28	-16	2.63	0.0085	15	7
	25 L	-8	24	-16	3.52	0.0004	16	4
	25 L	-8	24	-12	2.35	0.019	17	5
Paracingulate	9 R	16	32	28	2.89	0.0038	96	6
	9 R	12	48	24	2.67	0.0076	39	4
Posterior	31 R	8	-28	40	3.72	0.0002	29	3
	31 R	12	-32	36	3.10	0.0019	30	2
Frontal Cortex								
Dorsolateral Prefrontal Cortex	9 L	-28	36	28	4.00	0.0001	19	6
	10 L	-24	44	28	3.50	0.0005	23	5
	10 L	-36	48	12	2.63	0.0085	60	2
	46 R	40	36	12	2.56	0.0105	27	4
Dorsomedial Prefrontal Cortex	10 R	28	40	24	2.97	0.0030	49	1
	9 R	16	48	24	2.72	0.0065	101	3
	10 R	12	60	24	2.66	0.0077	63	2
Orbital Frontal Cortex	47 L	-24	8	-20	2.65	0.0081	19	4
	11 R	20	28	-16	3.10	0.0019	176	3
	47 R	28	16	-20	3.86	0.0001	15	5
	47 R	24	16	-20	3.44	0.0006	38	6
	47 R	20	20	-20	2.76	0.0057	19	2
Superior Frontal Gyrus	6 L	-12	-8	60	2.99	0.0028	15	2
Ventrolateral Prefrontal Cortex	* L	-40	44	4	2.53	0.0112	29	5
Ventromedial Prefrontal Cortex	10 N/A	0	64	-4	2.74	0.0062	19	1
	10 R	16	52	-12	2.31	0.0207	18	5
Fusiform Cortex								
Temporal, posterior division	20 L	-40	-12	-24	3.36	0.0008	20	2
	37 L	-36	-40	-12	2.32	0.0203	15	3
Temporal Occipital	37 L	-36	-52	-20	2.47	0.0133	20	1
Hippocampus	28 R	24	-28	-8	2.95	0.0032	45	2
	* R	32	-24	-12	2.64	0.0084	21	6
Insular Cortex	38 R	40	4	-16	2.63	0.0086	19	7
Intraparietal Sulcus								
Posterior division (hIP3)	31 L	-24	-52	36	3.41	0.0006	146	1
Lingual Gyrus	18 R	16	-56	0	3.40	0.0007	16	1
	30 R	24	-52	4	3.10	0.0019	31	3
Occipital Cortex								
Lateral, superior division	7 R	16	-72	44	2.80	0.0051	19	2
	7 R	12	-72	60	2.70	0.0069	31	3
	19 R	44	-68	48	2.96	0.0030	17	3
	39 R	52	-68	32	3.50	0.0005	37	1
Operculum Cortex								
Frontal	13 L	-36	24	4	2.41	0.0161	56	4
	13 R	40	20	4	2.51	0.0122	30	6
Parahippocampal Gyrus								
Posterior division	35 L	-16	-32	-24	2.88	0.0039	31	1
Postcentral Gyrus	3 R	60	-16	32	3.10	0.0019	20	2
	4 R	36	-20	40	2.83	0.0046	21	2
	7 R	16	-36	56	2.78	0.0054	22	2
Precentral Gyrus	6 L	-24	-12	60	3.32	0.0009	80	1
	6 L	-24	-20	64	2.66	0.0079	16	3
	6 L	-8	-32	76	2.63	0.0086	16	1
	6 R	4	-16	72	2.97	0.0030	35	4
	6 R	8	-20	68	2.75	0.0060	19	2
	6 R	12	-20	72	2.50	0.0124	17	3
	6 R	12	-20	76	2.47	0.0135	19	1
	9 R	56	4	20	2.43	0.015	19	6
	9 R	52	4	36	2.38	0.0171	15	3

Region	BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience								
Precuneus	5 L	-4	-48	68	3.26	0.0011	18	3
	5 L	-4	-48	68	2.57	0.0102	15	4
	7 L	-8	-68	52	2.67	0.0075	17	4
Superior Parietal Lobule	5 R	20	-44	60	2.70	0.0069	89	1
	5 R	28	-48	72	2.36	0.0181	27	3
	7 R	36	-52	64	2.42	0.0155	22	3
Temporal Cortex								
Middle, posterior division	21 R	60	-12	-16	2.95	0.0032	53	1
Planum Polare	38 L	-36	0	-24	2.70	0.0069	30	3
	38 R	40	0	-20	2.38	0.0174	42	3
Temporal Pole	38 R	44	12	-20	3.41	0.0007	30	2
	13 R	40	12	-20	2.73	0.0063	32	4
Supramarginal Gyrus								
Anterior division	40 L	-64	-36	24	3.96	0.0001	25	2
	40 L	-56	-32	40	3.61	0.0003	38	4
	40 L	-56	-40	32	2.73	0.0064	35	3
	2 R	60	-20	28	2.56	0.0105	30	3
Thalamus								
Pulvinar nucleus	* R	20	-24	16	3.04	0.0023	35	2
Negative Salience								
Cingulate Gyrus								
Anterior, dorsal	32 L	-12	28	24	-5.12	0.0000	2936	3
Anterior, ventral	25 R	12	20	-12	-2.52	0.0119	15	3
Paracingulate	10 L	-12	52	8	-4.22	0.0000	130	7
Posterior	29 L	-4	-48	16	-3.31	0.0009	101	1
	23 R	4	-20	24	-3.03	0.0024	19	1
	29 R	8	-40	12	-2.54	0.0111	17	3
Frontal Cortex								
Dorsolateral Prefrontal Cortex	10 L	-20	64	16	-3.08	0.0021	137	6
Orbital Frontal Cortex	11 L	-20	32	-16	-3.06	0.0022	16	5
	47 R	32	24	-12	-3.14	0.0017	15	4
Ventromedial Prefrontal Cortex	10 L	-16	56	-4	-3.14	0.0017	15	5
	10 R	28	52	8	-3.22	0.0013	86	6
	10 R	8	64	0	-2.71	0.0066	21	1
Fusiform Cortex								
Temporal Occipital	36 R	20	-40	-20	-2.47	0.0136	17	3
Intraparietal Sulcus								
Anterior division (hIP1)	40 L	-44	-52	36	-6.13	0.0000	8587	7
Posterior division (hIP3)	7 L	-28	-48	44	-6.10	0.0000	7939	6
Lingual Gyrus	19 R	16	-60	-8	-3.45	0.0006	20	1
Occipital Cortex								
Occipital Pole	17 L	-16	-96	4	-5.07	0.0000	3661	1
Lateral, superior division	19 L	-28	-88	12	-6.41	0.0000	5975	4
	19 R	28	-80	20	-5.68	0.0000	7068	5
	19 R	44	-80	8	-4.86	0.0000	1846	3
Operculum Cortex								
Parietal	13 L	-40	-32	20	-2.41	0.016	17	3
Parahippocampal Gyrus								
Anterior division	35 L	-16	-20	-20	-2.56	0.0103	43	3
Postcentral Gyrus	3 R	36	-32	56	-3.20	0.0014	20	1
Precentral Gyrus	6 L	-56	0	12	-4.48	0.0000	5886	2
	6 R	28	-8	64	-3.52	0.0004	54	1
	6 R	48	-4	40	-2.87	0.0041	37	1
	6 R	44	-8	44	-2.46	0.0137	17	5
Superior Parietal Lobule	7 R	20	-56	56	-3.14	0.0017	21	1
Supplementary Motor Cortex	6 R	4	-8	52	-3.90	0.0001	604	1
Temporal Cortex								
Inferior, posterior division	20 R	44	-12	-24	-3.70	0.0002	47	1
Middle, posterior division	20 R	48	-8	-24	-3.13	0.0018	32	4

Table A.11. Foci of Activation from Mean-Centering PLS Analysis Comparing Individuals with High-Functioning Autism to Neurotypical Controls.

Mean-centering task-PLS was used to identify neural networks that were differentially engaged in response to the task conditions in both the neurotypical and the high-functioning autism groups. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Angular Gyrus									
	L	39	-48	-60	20	3.686	0.0002	20	7
	L	40	-60	-52	20	3.229	0.0012	21	6
Pga	L	39	-44	-60	16	4.164	0.0000	22	6
	R	22	64	-48	16	3.312	0.0009	16	5
Cerebellum									
Crus II	R	*	8	-76	-36	4.464	0.0000	15	6
Lobule I-IV	L	*	-20	-32	-32	3.453	0.0006	16	6
Lobule VI	R	*	24	-60	-24	4.137	0.0000	17	1
Cingulate Cortex									
Anterior, dorsal	L	24	-8	4	36	3.723	0.0002	407	3
	R	24	4	4	28	3.193	0.0014	730	4
Frontal Cortex									
Dorsolateral Prefrontal Cortex	R	9	52	20	20	2.644	0.0082	37	5
	R	13	40	28	12	3.021	0.0025	16	2
Dorsomedial Prefrontal Cortex	R	10	12	56	8	2.328	0.0199	17	1
Middle Frontal Gyrus	L	6	-32	8	56	4.219	0.0000	916	7
Ventromedial Prefrontal Cortex	L	10	-16	56	4	4.068	0.0000	54	3
	L	10	-24	56	0	3.314	0.0009	40	2
	L	10	-20	56	4	2.961	0.0031	58	1
	L	10	-20	60	-4	2.654	0.0080	24	5
Fusiform Cortex									
Occipital	R	37	44	-64	-24	4.761	0.0000	21	1
Temporal Occipital	R	20	36	-40	-24	2.413	0.0158	19	4
Temporal Occipital (FFA)	R	37	44	-44	-24	3.792	0.0001	16	7
Hippocampus	L	35	-16	-20	-20	4.219	0.0000	20	2
Insular Cortex	L	13	-32	20	4	3.926	0.0001	15	2
Occipital Cortex									
Lateral, inferior division	L	19	-56	-64	-4	3.689	0.0002	29	5
	L	37	-44	-64	-4	4.020	0.0001	22	6
	L	37	-52	-68	-4	3.968	0.0001	27	7
	R	19	48	-72	-20	3.157	0.0016	16	2
Lateral, superior division	L	39	-40	-64	20	4.490	0.0000	21	5
Opercular Cortex									
Central	L	13	-40	-4	12	2.911	0.0036	19	6
Parietal	R	40	44	-32	32	2.707	0.0068	37	6
Parahippocampal Gyrus									
Posterior division	R	35	20	-24	-28	3.549	0.0004	44	3
	R	36	24	-28	-20	5.288	0.0000	57	2
Postcentral Gyrus	L	40	-52	-24	48	4.300	0.0000	1043	6
Precentral gyrus	N/A	6	0	-24	68	2.771	0.0056	16	7
Superior Parietal Lobule	L	7	-20	-48	68	2.507	0.0122	17	6
	R	7	12	-52	64	3.388	0.0007	30	5
	R	7	16	-52	68	3.425	0.0006	38	4

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Supramarginal Gyrus									
Posterior division	L	22	-64	-40	20	4.106	0.0000	20	5
Temporal Cortex									
Middle, anterior	R	38	52	4	-28	3.973	0.0001	29	1
Planum Polare	R	21	44	-8	-12	6.574	0.0000	50	3
	R	38	44	4	-20	5.157	0.0000	152	2
Temporal Pole	R	22	56	8	0	2.402	0.0163	15	1
Negative Salience									
Amygdala/Hippocampus	L	*	-12	-12	-16	-6.580	0.0000	133	2
Caudate	L	*	-20	20	12	-8.275	0.0000	6358	2
	L	*	-16	16	12	-7.396	0.0000	10163	5
Cerebellum									
Lobule VI	L	*	-24	-48	-28	-4.468	0.0000	19	1
Cingulate Cortex									
Anterior, ventral	N/A	25	0	20	-8	-9.217	0.0000	11222	4
Posterior	L	31	-4	-32	32	-9.163	0.0000	9868	3
	R	29	12	-44	8	-3.420	0.0006	16	1
Frontal Cortex									
Dorsolateral Prefrontal Cortex	R	9	44	8	40	-3.625	0.0003	64	6
Middle Frontal Gyrus	R	8	36	24	44	-4.728	0.0000	114	5
Superior Frontal Gyrus	L	6	-4	12	68	-6.410	0.0000	54	6
	L	6	-24	8	60	-2.552	0.0107	23	4
	L	8	-24	24	40	-3.745	0.0002	20	2
	L	24	-20	4	48	-3.610	0.0003	16	5
	R	8	16	28	52	-6.711	0.0000	19	5
	R	9	8	52	28	-8.772	0.0000	9989	7
Ventromedial Prefrontal Cortex	R	11	4	32	-16	-2.994	0.0028	20	1
Fusiform Cortex									
Temporal Occipital (FFA)	L	37	-24	-52	-20	-8.762	0.0000	10293	6
Temporal, posterior division	L	20	-40	-28	-20	-3.670	0.0002	30	1
Hippocampus	L	*	-28	-24	-16	-4.673	0.0000	66	1
Occipital Cortex									
Lateral, inferior division	L	18	-28	-88	-24	-3.446	0.0006	22	2
Parahippocampal Gyrus									
Anterior division	R	34	16	-8	-28	-4.039	0.0001	38	1
	R	35	20	-12	-32	-3.108	0.0019	15	2
Postcentral Gyrus	L	7	-8	-44	64	-5.050	0.0000	30	1
	R	3	60	-12	24	-4.614	0.0000	41	1
Precentral gyrus	L	6	-36	-4	48	-6.653	0.0000	24	7
	L	6	-44	4	40	-3.921	0.0001	22	5
	L	6	-40	-4	52	-3.434	0.0006	30	6
Precuneus Cortex	N/A	5	0	-48	60	-3.708	0.0002	21	2
Supplementary Motor Cortex	L	6	-12	-16	52	-7.370	0.0000	5115	1

Table A.12. Foci of Activation from Seed-PLS Analysis of Neural Networks Functionally Connected to the Right OFC in Individuals with High-Functioning Autism

Regions comprising the functional network associated with right OFC activity and its interaction with RT in participants with high-functioning autism. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Amygdala	R	*	28	4	-20	5.914	0.0000	193	2
Caudate	R	*	16	24	-4	4.107	0.0000	59	2
	R	*	20	12	20	3.743	0.0002	28	2
	R	*	16	8	12	2.905	0.0037	21	6
Cerebellum									
Crus I	L	*	-12	-68	-32	4.248	0.0000	17	5
	L	*	-12	-72	-28	3.574	0.0004	22	2
Lobule V	N/A	*	0	-60	-20	6.634	0.0000	26	4
	R	*	4	-56	-16	4.772	0.0000	21	6
Lobule VI	L	*	-32	-44	-28	3.232	0.0012	15	3
	L	*	-8	-60	-24	5.758	0.0000	24	2
	L	*	-28	-44	-40	5.208	0.0000	18	5
Cingulate Cortex									
Anterior, dorsal	R	24	8	8	36	5.866	0.0000	39	2
Paracingulate	L	24	-16	4	48	4.391	0.0000	88	7
Frontal Cortex									
Dorsolateral Prefrontal Cortex	L	9	-32	20	32	3.580	0.0003	23	2
	L	9	-44	24	32	3.031	0.0024	46	7
	L	*	-32	16	24	3.157	0.0016	50	3
	R	9	40	12	40	4.729	0.0000	418	4
	R	9	40	8	40	4.023	0.0001	68	7
	R	13	40	20	20	4.013	0.0001	33	7
Dorsomedial Prefrontal Cortex	L	8	-12	40	44	3.043	0.0023	18	3
	L	10	-8	68	16	3.520	0.0004	21	6
Middle Frontal Gyrus	L	6	-32	8	52	3.445	0.0006	20	7
	R	6	36	12	44	4.737	0.0000	277	5
	R	8	24	32	36	2.809	0.0050	34	5
Superior Frontal Gyrus	L	6	-8	20	60	3.239	0.0012	118	6
	L	8	-24	12	52	3.678	0.0002	17	3
Ventromedial Prefrontal Cortex	L	10	-4	56	-16	4.770	0.0000	32	1
	R	10	28	56	0	3.655	0.0003	38	6
Fuisform Cortex									
Temporal, posterior division	R	20	44	-36	-24	5.737	0.0000	43	7
	R	20	44	-36	-24	4.033	0.0001	26	6
	R	20	44	-36	-24	3.755	0.0002	37	5
Occipital	L	18	-24	-80	-8	5.234	0.0000	16	4
	L	18	-20	-80	-8	3.937	0.0001	28	2
	R	18	32	-84	-12	4.358	0.0000	18	7
	R	18	32	-84	-16	4.330	0.0000	42	6
Temporal Occipital (FFA)	L	37	-44	-48	-20	4.683	0.0000	20	7
	L	37	-24	-48	-12	4.343	0.0000	17	5
Temporal, posterior division	R	36	36	-28	-24	3.859	0.0001	20	3
Temporal, posterior division (FFA)	L	37	-44	-44	-20	3.705	0.0002	17	5
Insular Cortex	R	*	36	-12	-8	4.022	0.0001	26	1

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Positive Salience									
Intraparietal Sulcus									
Anterior (hIP1)	R	40	40	-44	40	3.583	0.0003	67	5
	R	40	40	-48	36	2.964	0.0030	25	3
Anterior (hIP2)	R	40	40	-32	36	3.994	0.0001	99	6
	R	40	40	-32	36	3.188	0.0014	58	7
Occipital Cortex									
Lateral, inferior division	L	19	-56	-64	-4	3.172	0.0015	23	5
	R	19	52	-72	-12	4.633	0.0000	24	7
	R	19	44	-80	-8	4.150	0.0000	26	5
Lateral, superior division	L	19	-32	-80	12	5.119	0.0000	15	5
	R	7	24	-64	60	3.885	0.0001	42	6
	R	7	24	-60	52	3.278	0.0010	40	7
Occipital Pole	R	18	36	-92	-12	3.391	0.0007	53	2
Opercular Cortex									
Central	R	6	60	0	8	3.873	0.0001	18	3
	R	43	52	-12	20	4.758	0.0000	209	6
Parietal	L	41	-48	-28	16	3.645	0.0003	15	2
Parahippocampal Gyrus									
Anterior division	R	35	24	-20	-28	3.333	0.0009	18	2
Posterior division	R	35	16	-32	-12	3.981	0.0001	36	4
Precentral gyrus	L	6	-40	-4	32	5.349	0.0000	18	2
	L	6	-24	-16	64	4.849	0.0000	45	5
	L	6	-24	-16	60	4.371	0.0000	52	4
	L	6	-24	-8	68	3.457	0.0005	23	7
	R	6	20	-12	64	4.081	0.0000	19	5
	R	44	48	8	20	3.779	0.0002	99	3
Putamen	L	*	-20	-4	8	3.427	0.0006	17	2
	R	*	20	0	8	5.168	0.0000	23	1
Superior Parietal Lobule	L	40	-40	-40	56	3.297	0.0010	15	5
	R	7	20	-52	64	4.067	0.0000	28	5
Supplementary Motor Cortex	L	6	-8	-12	56	4.034	0.0001	106	3
	L	24	-12	4	48	4.130	0.0000	80	5
	L	24	-8	4	48	3.940	0.0001	203	4
Supramarginal Gyrus									
Anterior division	L	40	-52	-28	28	4.634	0.0000	340	5
Posterior division	L	40	-60	-44	20	5.468	0.0000	15	4
Temporal Cortex									
Planum Temporale	L	22	-60	-40	20	4.850	0.0000	18	5
Middle, temporooccipital part	R	39	44	-52	12	2.969	0.0030	15	7
Superior, posterior division	R	22	64	-8	0	3.724	0.0002	16	5
Temporal Pole	R	21	48	8	-28	4.192	0.0000	23	1
	R	38	44	12	-24	4.486	0.0000	23	3
Thalamus Ventral Anterior Nucleus									
Ventral Anterior Nucleus	R	*	12	-4	12	3.019	0.0025	19	3

Table A.13. Foci of Activation from Positive Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Right dlPFC in Individuals with High-Functioning Autism

Regions comprising the functional network associated with the right dlPFC activity and its interaction with RT in individuals with high-functioning autism. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Negative Salience									
Amygdala/Hippocampus	L	*	-12	-12	-16	-4.0486	0.0001	49	6
Angular Gyrus	R	40	56	-48	44	-3.789	0.0002	31	7
Caudate	L	*	-8	8	8	-4.9741	0.0000	73	1
	L	*	-20	20	12	-3.4436	0.0006	18	2
	L	*	-12	4	12	-3.4366	0.0006	26	2
	L	*	-16	-4	24	-3.4222	0.0006	40	2
Cerebellum									
Crus I	L	*	-8	-80	-28	-5.375	0.0000	104	1
	L	*	-32	-60	-32	-4.2773	0.0000	31	4
	R	*	28	-80	-20	-3.7756	0.0002	19	4
	R	*	36	-60	-36	-5.2281	0.0000	28	4
	R	*	40	-52	-32	-4.3783	0.0000	29	3
Vermis VI	N/A	*	0	-84	-16	-4.4845	0.0000	28	4
Vermis VIIIa	L	*	-4	-68	-36	-3.7148	0.0002	19	5
Vermis VIIIb	R	*	4	-60	-36	-5.5499	0.0000	22	3
Cingulate Cortex									
Anterior, dorsal	L	23	-4	-16	32	-7.5892	0.0000	1618	2
	R	24	8	-12	40	-5.514	0.0000	68	1
	R	24	4	4	24	-3.8282	0.0001	55	2
Anterior, ventral	R	25	4	20	0	-4.4903	0.0000	22	5
Paracingulate	L	10	-4	52	-4	-10.576	0.0000	1210	3
	L	10	-8	44	-8	-4.7346	0.0000	22	2
	R	10	8	52	-4	-7.9868	0.0000	30	1
Posterior	R	29	4	-48	4	-6.5723	0.0000	2507	4
Frontal Cortex									
Dorsolateral Prefrontal Cortex	L	9	-36	36	28	-5.9474	0.0000	819	5
	L	10	-36	44	28	-6.7543	0.0000	16	2
	R	9	48	20	40	-2.997	0.0027	16	3
	R	10	40	44	16	-3.8427	0.0001	24	7
	R	10	40	48	16	-3.1085	0.0019	25	5
	R	46	40	48	8	-2.9784	0.0029	113	4
Dorsomedial Prefrontal Cortex	R	10	8	64	12	-5.4169	0.0000	80	2
Middle Frontal Gyrus	L	6	-32	0	60	-4.9408	0.0000	19	1
	R	6	36	12	56	-3.3836	0.0007	25	5
Orbital Frontal Cortex	L	47	-32	24	-4	-5.3827	0.0000	1063	7
Superior Frontal Gyrus	L	9	-8	52	32	-6.2184	0.0000	157	1
	R	6	8	12	64	-6.2138	0.0000	62	3
	R	6	8	8	68	-4.4266	0.0000	50	5
	R	6	28	4	64	-2.9477	0.0032	24	4
Ventrolateral Prefrontal Cortex	L	10	-40	48	12	-5.5608	0.0000	94	2
	L	44	-48	8	8	-2.9216	0.0035	17	6
	R	44	60	16	12	-4.0929	0.0000	36	1
	R	45	56	20	12	-4.2496	0.0000	89	6
	R	46	48	40	8	-6.865	0.0000	42	1
	R	47	36	36	4	-3.3463	0.0008	71	7
	R	*	36	52	4	-4.0709	0.0000	15	2
Fusiform Cortex									
Occipital	L	19	-40	-72	-16	-4.8712	0.0000	26	1
	L	19	-32	-72	-20	-4.3627	0.0000	23	6
	L	19	-28	-80	-16	-3.7989	0.0001	21	4
	L	19	-36	-72	-16	-3.7476	0.0002	16	7
Temporal Occipital (FFA)	L	37	-32	-56	-20	-3.4307	0.0006	15	3
	R	37	40	-56	-12	-5.1501	0.0000	80	5
	R	37	40	-60	-20	-2.7696	0.0056	18	7
Heschl's Gyrus	L	22	-48	-20	4	-4.2414	0.0000	103	6
Hippocampus	L	*	-24	-16	-20	-3.5362	0.0004	28	7
Insular Cortex	L	13	-44	0	0	-4.7196	0.0000	41	5
	R	47	36	20	0	-3.367	0.0008	34	5
Intraparietal Sulcus									
Anterior (hIP1)	R	*	36	-44	28	-5.47	0.0000	71	1
Lingual Gyrus	L	17	-20	-84	4	-5.7067	0.0000	2025	7
	L	18	-4	-88	-12	-4.0877	0.0000	15	7
	L	18	-8	-88	-12	-4.0613	0.0000	29	2
	L	19	-20	-52	-4	-4.8657	0.0000	32	3
	R	18	12	-76	-12	-3.3432	0.0008	20	7
	R	*	16	-68	0	-3.6713	0.0002	22	2

Region		BA	X	Y	Z	BSR	p-value	Size	Lag
Negative Salience									
Occipital Cortex									
Lateral, inferior division	L	37	-44	-64	-4	-3.7731	0.0002	26	1
	R	19	52	-68	-20	-3.9026	0.0001	26	6
	R	37	48	-60	-4	-4.2531	0.0000	90	4
	R	39	52	-72	12	-3.2666	0.0011	22	4
Lateral, superior division	L	19	-56	-64	20	-4.1055	0.0000	15	7
	L	39	-48	-72	16	-4.9247	0.0000	15	5
	L	39	-44	-68	28	-3.5201	0.0004	22	2
	R	7	12	-72	56	-3.345	0.0008	18	7
	R	39	48	-72	24	-3.7228	0.0002	19	7
	R	39	48	-64	16	-2.7768	0.0055	33	6
Occipital Pole	R	18	4	-92	-16	-4.6037	0.0000	71	6
	R	18	20	-92	12	-3.7991	0.0001	28	6
	R	18	20	-92	12	-3.1382	0.0017	16	7
	R	19	28	-92	4	-3.4146	0.0006	16	1
Opercular Cortex									
Central	L	41	-56	-16	12	-4.6857	0.0000	15	2
	L	41	-60	-20	12	-3.6956	0.0002	19	7
	R	13	44	-4	8	-4.0749	0.0000	17	4
	R	13	40	-12	20	-2.5337	0.0113	17	4
	R	22	48	-4	4	-3.2111	0.0013	18	2
	R	22	56	0	4	-3.0309	0.0024	18	5
Parietal	L	13	-36	-32	24	-2.6287	0.0086	34	5
Parahippocampal Gyrus									
Anterior division	R	35	20	-12	-32	-3.5329	0.0004	19	4
Postcentral Gyrus	L	7	-8	-44	68	-5.4654	0.0000	37	1
	R	40	48	-36	60	-3.3184	0.0009	42	5
Precentral gyrus	L	4	-16	-28	68	-3.1661	0.0015	17	6
	L	6	-20	-20	76	-5.4262	0.0000	29	5
	L	6	-36	-12	64	-4.6114	0.0000	48	3
	L	6	-32	-24	72	-4.257	0.0000	27	7
	R	4	52	-8	48	-3.9193	0.0001	35	3
	R	6	48	-8	36	-4.0093	0.0001	26	4
	R	6	60	-4	36	-3.9264	0.0001	59	5
	R	6	24	-20	52	-3.7635	0.0002	16	1
	R	6	56	4	40	-3.7072	0.0002	16	7
	R	6	36	-8	52	-3.1298	0.0017	35	6
Precuneus Cortex	L	30	-20	-56	16	-5.7188	0.0000	1992	5
	N/A	5	0	-40	52	-8.6551	0.0000	3803	3
	R	7	4	-72	44	-7.8591	0.0000	2147	1
	R	30	20	-48	8	-6.6131	0.0000	2070	6
Putamen	R	*	28	4	-4	-4.2954	0.0000	36	2
	R	*	32	-8	0	-3.0049	0.0027	16	4
Supplementary Motor Cortex	R	6	4	-12	72	-4.5584	0.0000	20	1
	R	6	8	8	64	-4.2984	0.0000	37	6
	R	6	8	-4	64	-3.9962	0.0001	19	7
Supracalcarine Cortex	R	31	24	-64	20	-3.4667	0.0005	17	2
Supramarginal Gyrus									
Posterior division	R	13	52	-40	24	-5.9164	0.0000	46	2
	R	40	52	-36	48	-3.4645	0.0005	40	6
	R	40	60	-44	24	-3.3643	0.0008	15	4
Temporal Cortex									
Middle, posterior division	L	21	-56	-40	-4	-3.5009	0.0005	23	4
Planum Temporale	L	41	-60	-20	8	-3.9298	0.0001	97	4
Superior, anterior division	L	21	-56	-8	-4	-3.6598	0.0003	35	7
Inferior, temporooccipital part	R	37	48	-56	-4	-3.6802	0.0002	27	6
Middle, temporooccipital part	R	39	44	-56	8	-3.5616	0.0004	43	2
Superior, poterior division	R	42	64	-32	12	-5.1798	0.0000	66	4
	R	42	64	-32	8	-2.8669	0.0041	23	5
	R	*	56	-28	0	-4.3836	0.0000	30	3
Thalamus	L	*	-20	-20	0	-3.1784	0.0015	20	5

Table A.14. Foci of Activation from Negative Salience Network in Seed-PLS Analysis of Neural Networks Functionally Connected to the Right dlPFC in Individuals with High-Functioning Autism

Regions comprising the functional network associated with the right dlPFC activity and its interaction with RT in individuals with high-functioning autism. Clusters were considered significant if they had a peak voxel with a BSR of at least $\pm$ 2.3 ($p < 0.02$), if they were a minimum of 10mm away from other peak voxels, and if the cluster contained 15 contiguous voxels.

APPENDIX B. SUPPLEMENTARY FIGURES

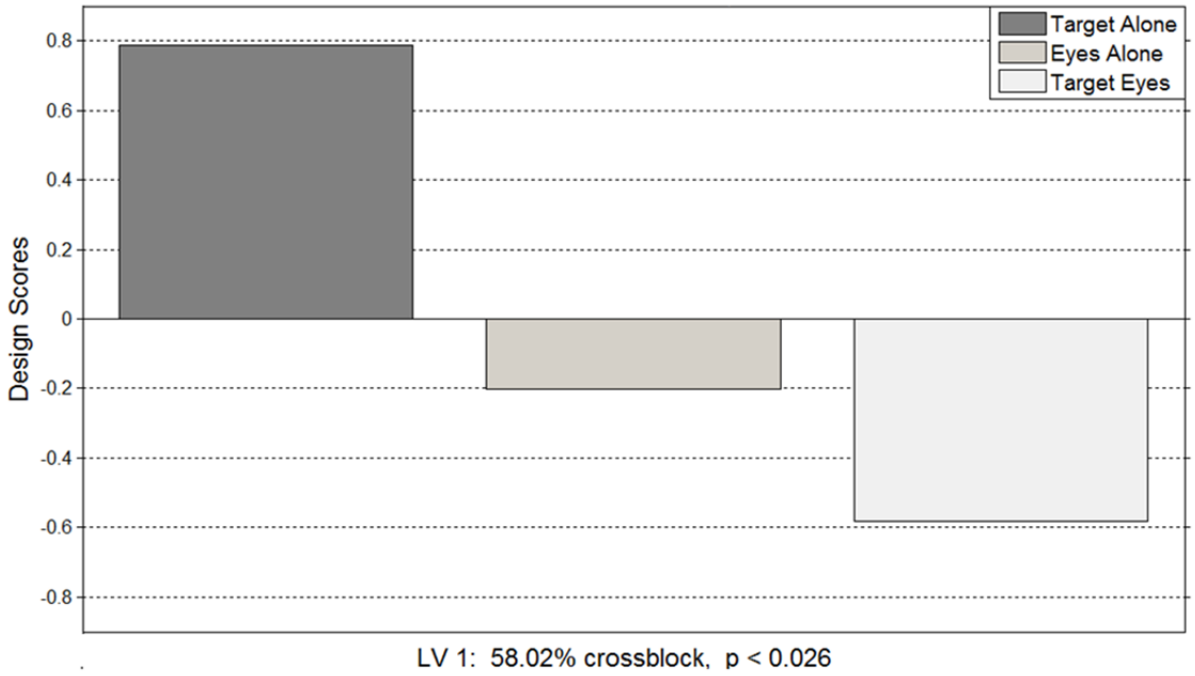

Figure B.1. Design Salience Scores from Mean-Centering Task-PLS in Neurotypical Participants

Graph values are design scores for N = 13 neurotypical participants. Mean-centering task-PLS was used to identify neural networks that reliably discriminate between task conditions. This analysis identified a single significant latent variable (LV1) that described 58.02% of the crossblock covariance and was associated with a neural network that reliably ($p < 0.026$ by permutation test) discriminated between the Eyes Alone and Target Eyes conditions as compared to the Target Alone condition.

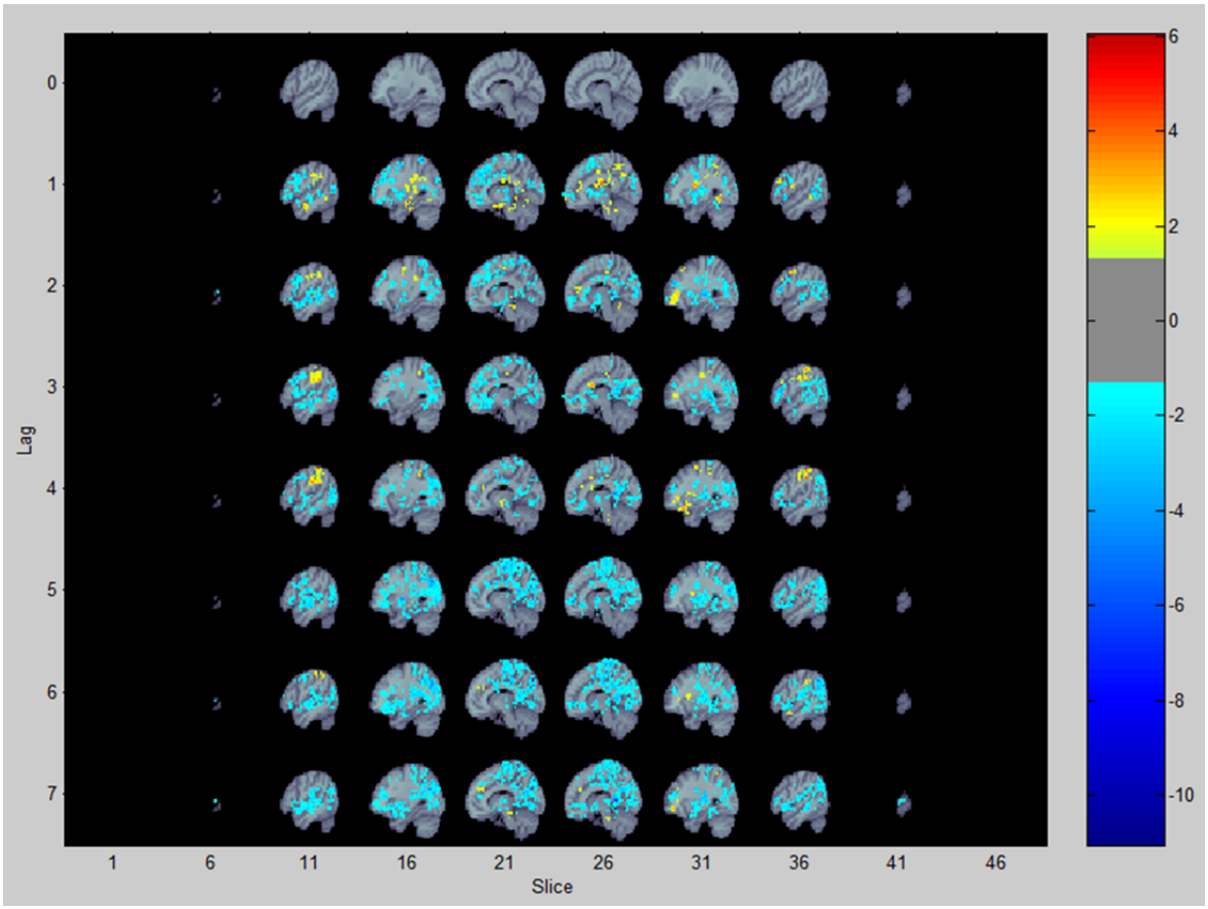

Figure B.2. Activation Map Displaying Regions Differentiating between Task Conditions from LV1 of the Task-PLS Analysis in the Neurotypical Participants.

Task-PLS activation map for the neurotypical participants. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

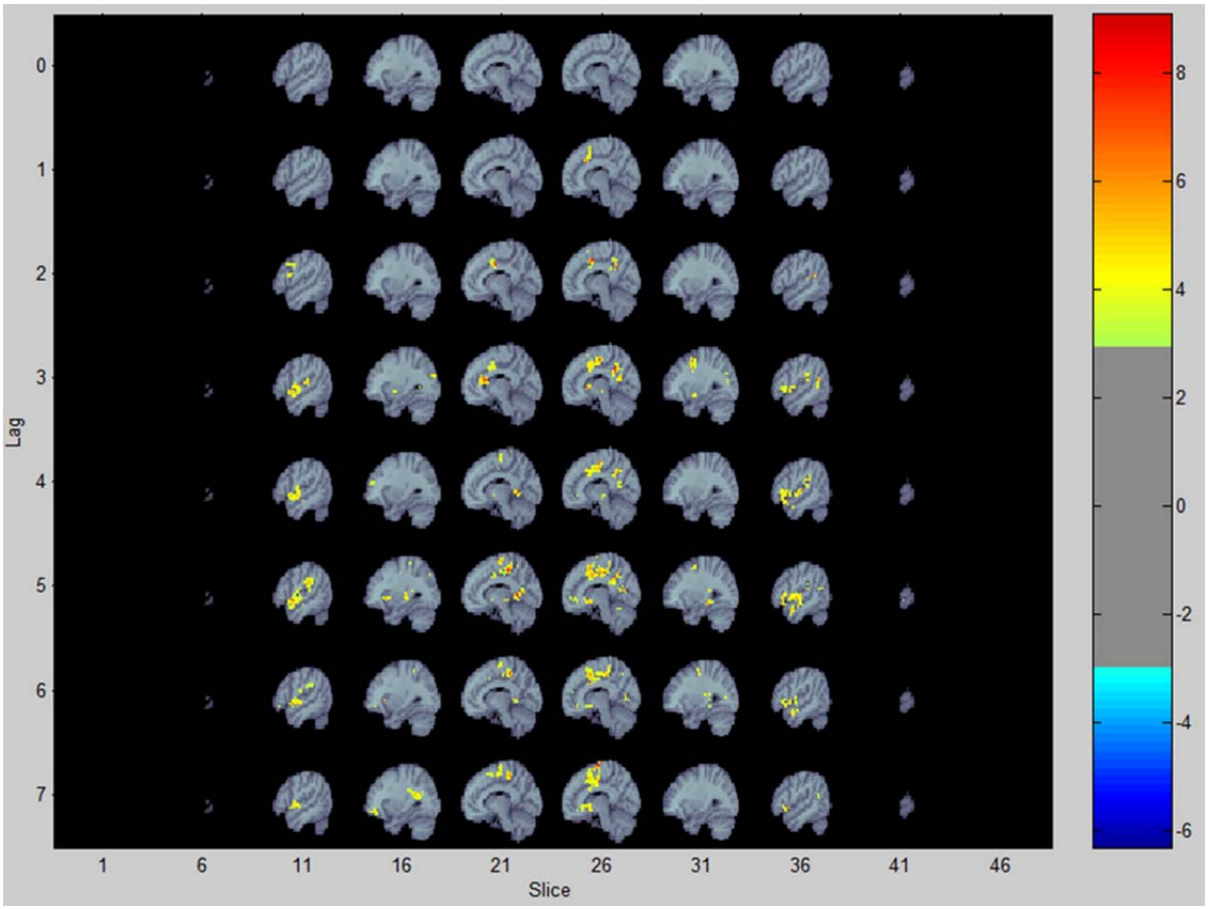

Figure B.3. Activation Map Displaying Neural Networks Functionally Connected to the Right OFC in the Neurotypical Participants.

LV1 of seed-PLS activation map representing functional connectivity with the right OFC for the neurotypical participants. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

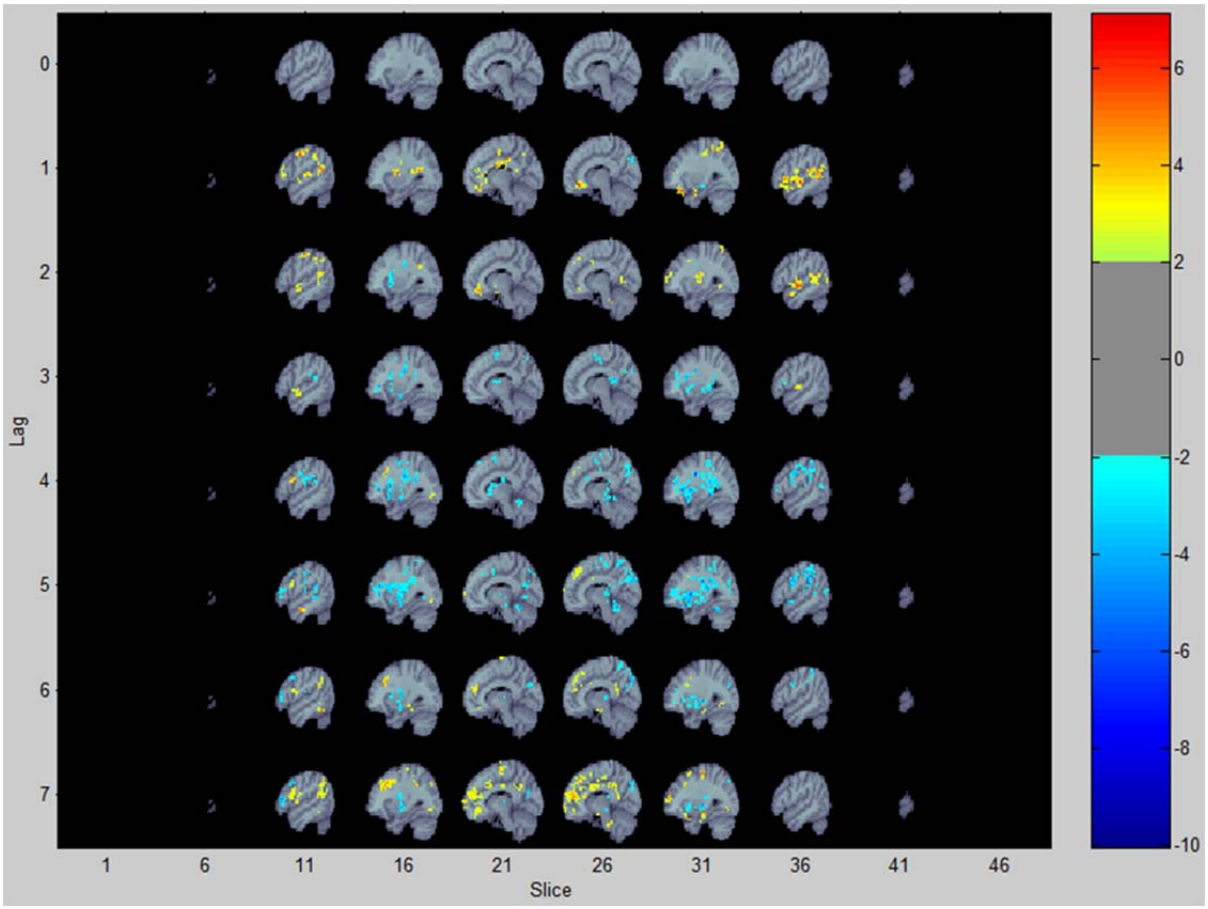

Figure B.4. Activation Map Displaying Neural Networks Functionally Connected to the Left vlPFC in the Neurotypical Participants.

LV2 of seed-PLS activation map representing functional connectivity with the left vlPFC for the neurotypical participants. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

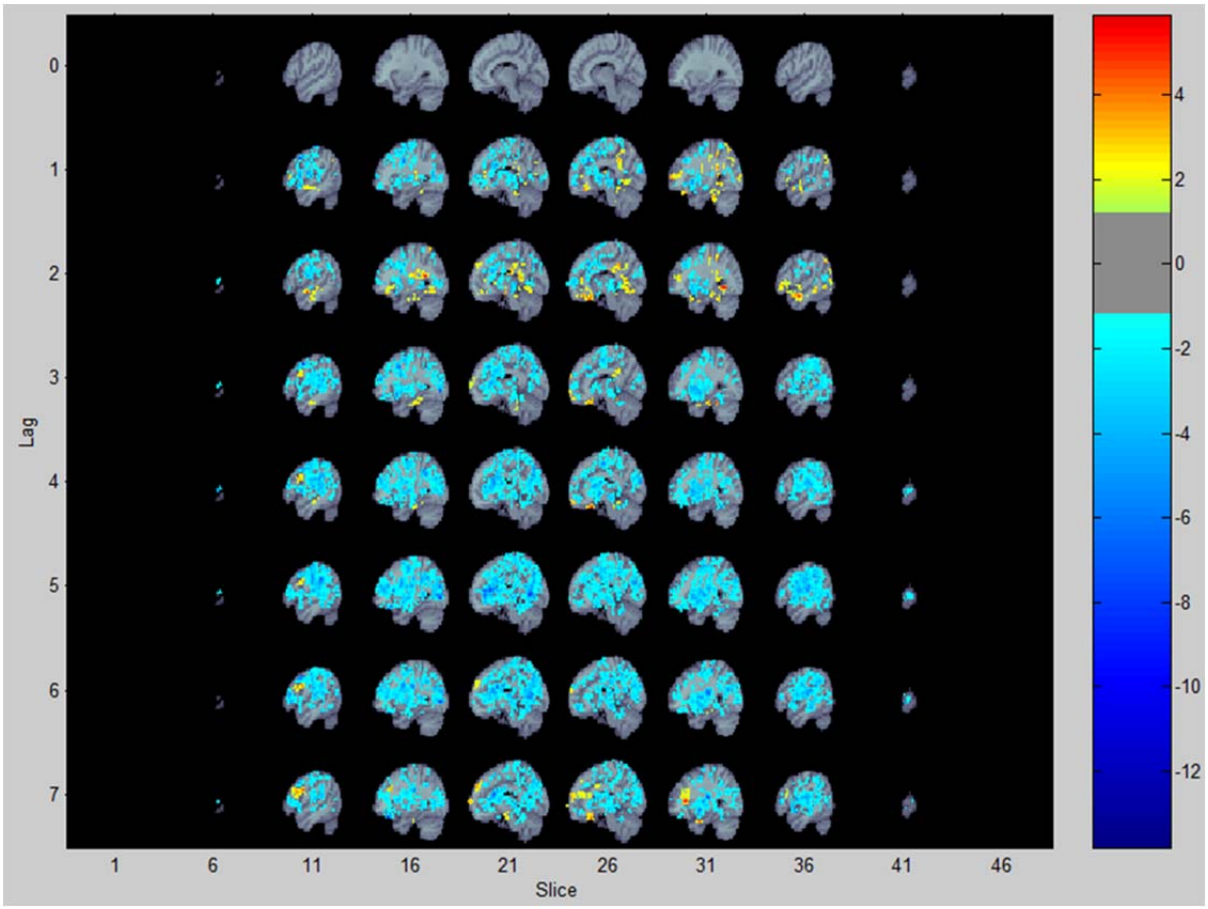

Figure B.5. Activation Map Displaying Neural Networks Functionally Connected to Right dlPFC in the Neurotypical Participants.

LV1 of seed-PLS activation map representing functional connectivity with the right dlPFC for the neurotypical participants. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

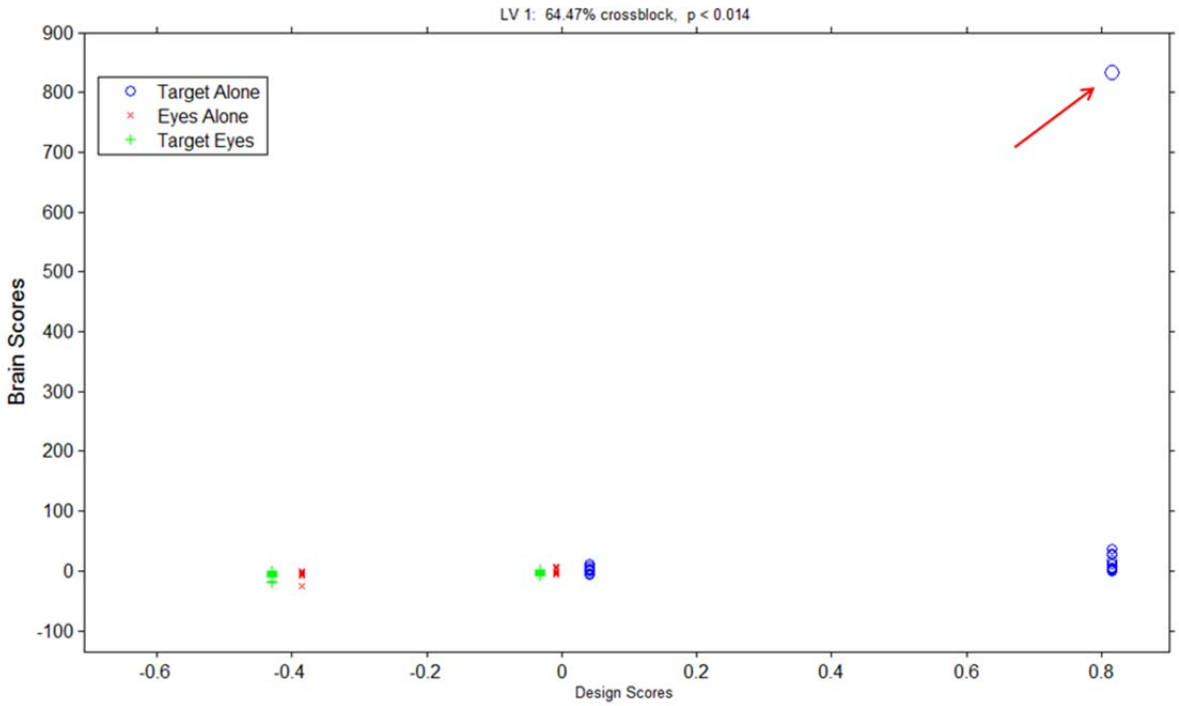

Figure B.6. Outlier Brain Score from Participant with High-Functioning Autism in the Between Group Task-PLS Analysis

Brain scores from the original between group Task-PLS analysis for individual participants. The red arrow indicates the brain score of the participant whose data was excluded because of a highly abnormal brain score that skewed the analysis.

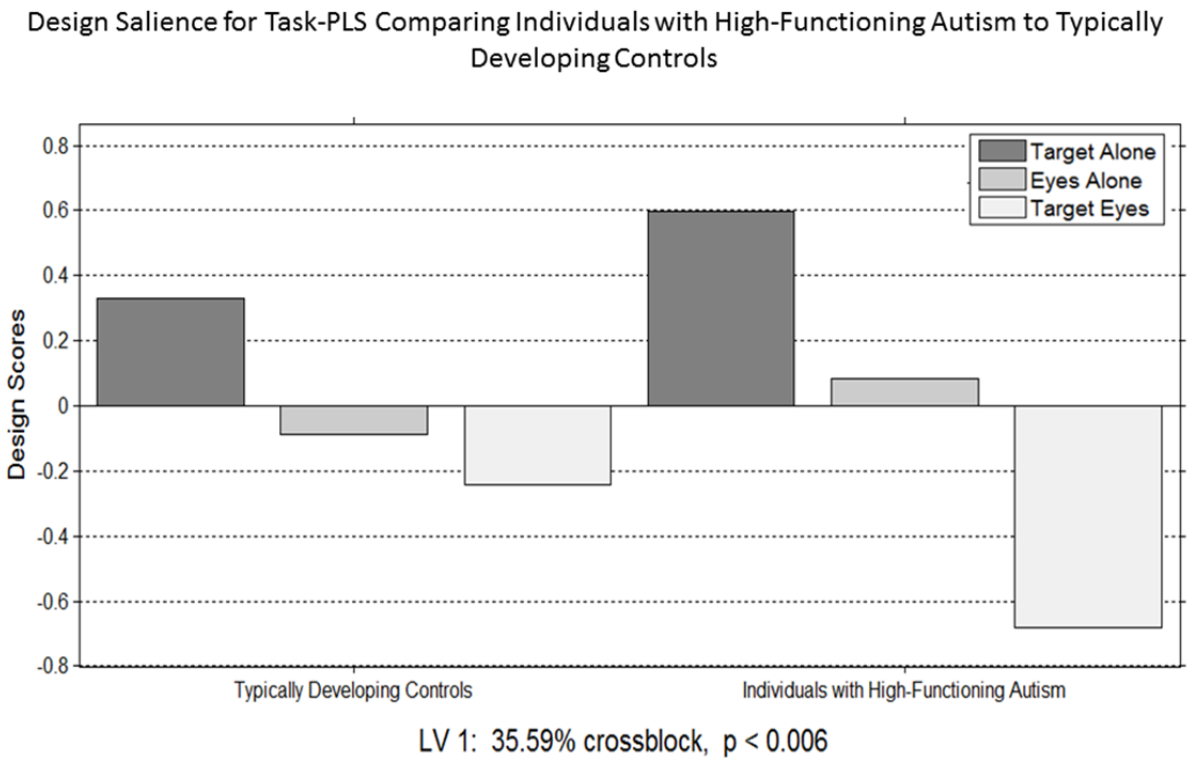

Figure B.7. Design Salience Scores from Mean-Centering Task-PLS Comparing Individuals with High-Functioning Autism to Neurotypical Participants

Graph values are task-PLS design scores for N = 14 neurotypical participants and N = 13 individuals with high-functioning autism. This analysis identified a latent variable (LV1) that explained 35.59% of the crossblock covariance ($p < 0.006$ by permutation test). The positive salience network associated with this LV was differentially involved in processing the Target Alone condition and the negative salience network was involved in processing the Target Eyes conditions in both groups, however the level of discrimination in the individuals with autism was nearly double that of the neurotypical group.

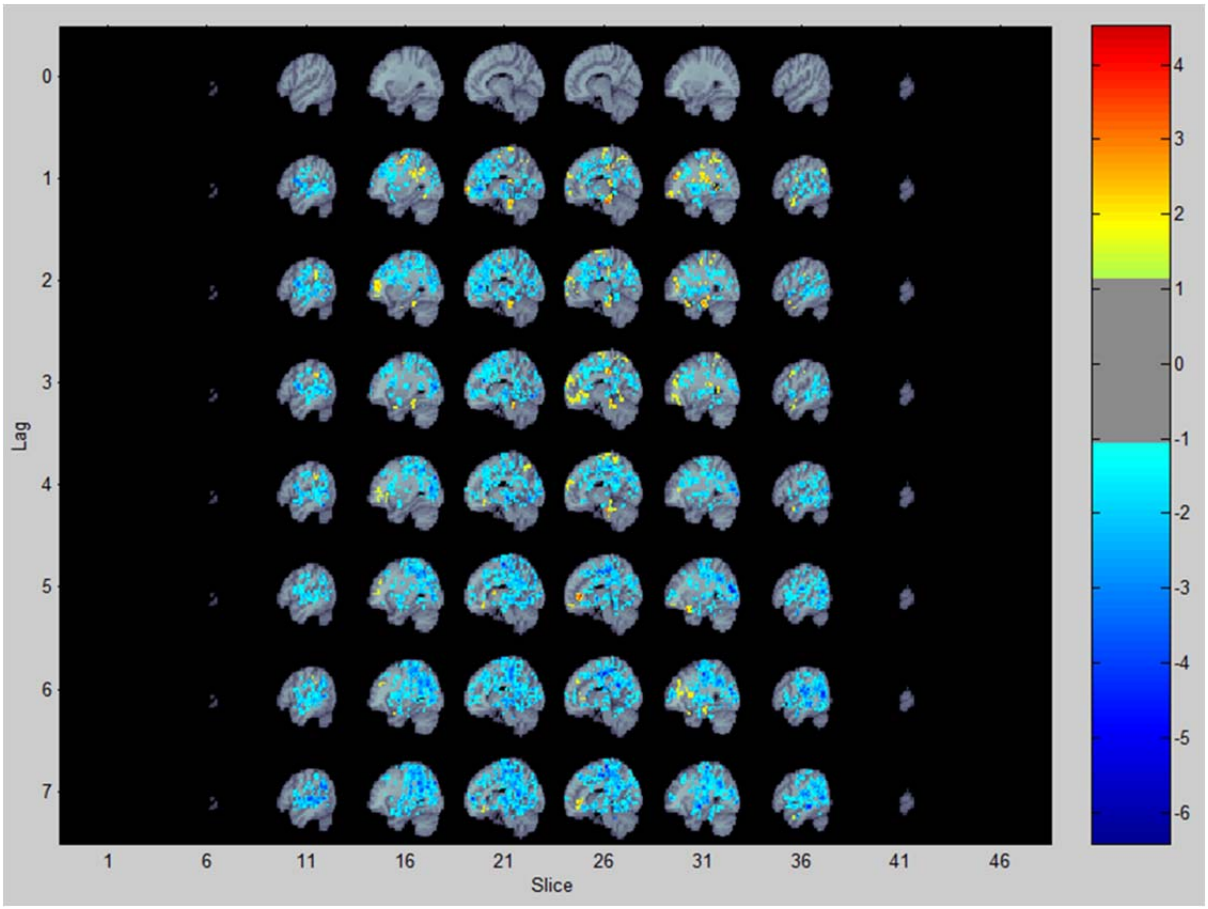

Figure B.8. Activation Map Displaying Regions Differentiating between Task Conditions from the Task-PLS Analysis on the Comparison between Individuals with Autism.

LV1 of task-PLS activation map of regions differentiating between conditions in each group. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

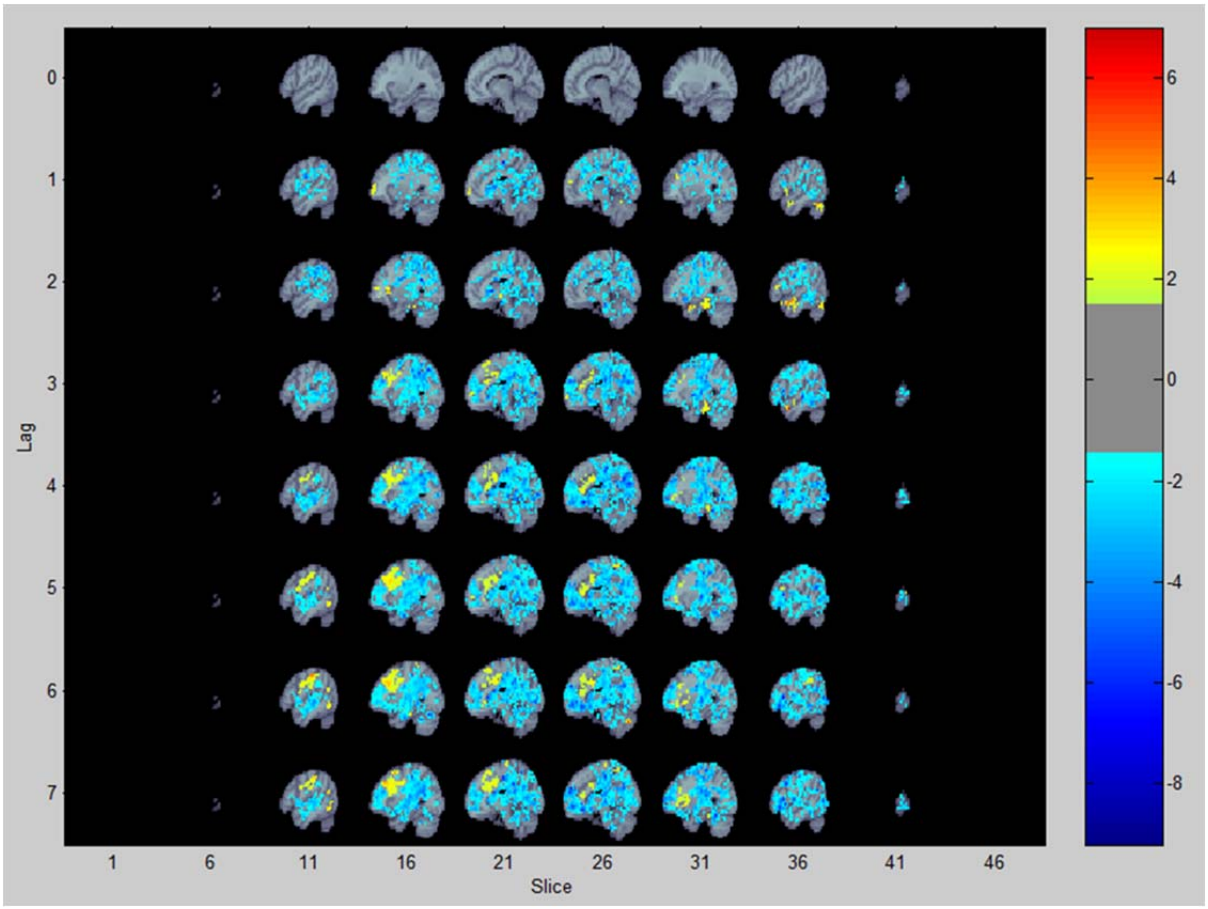

Figure B.9. Activation Map Displaying Regions Functionally Connected to the Right OFC in Individuals with Autism.

LV1 of seed-PLS activation map of functional connectivity with the right OFC for individuals with autism. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

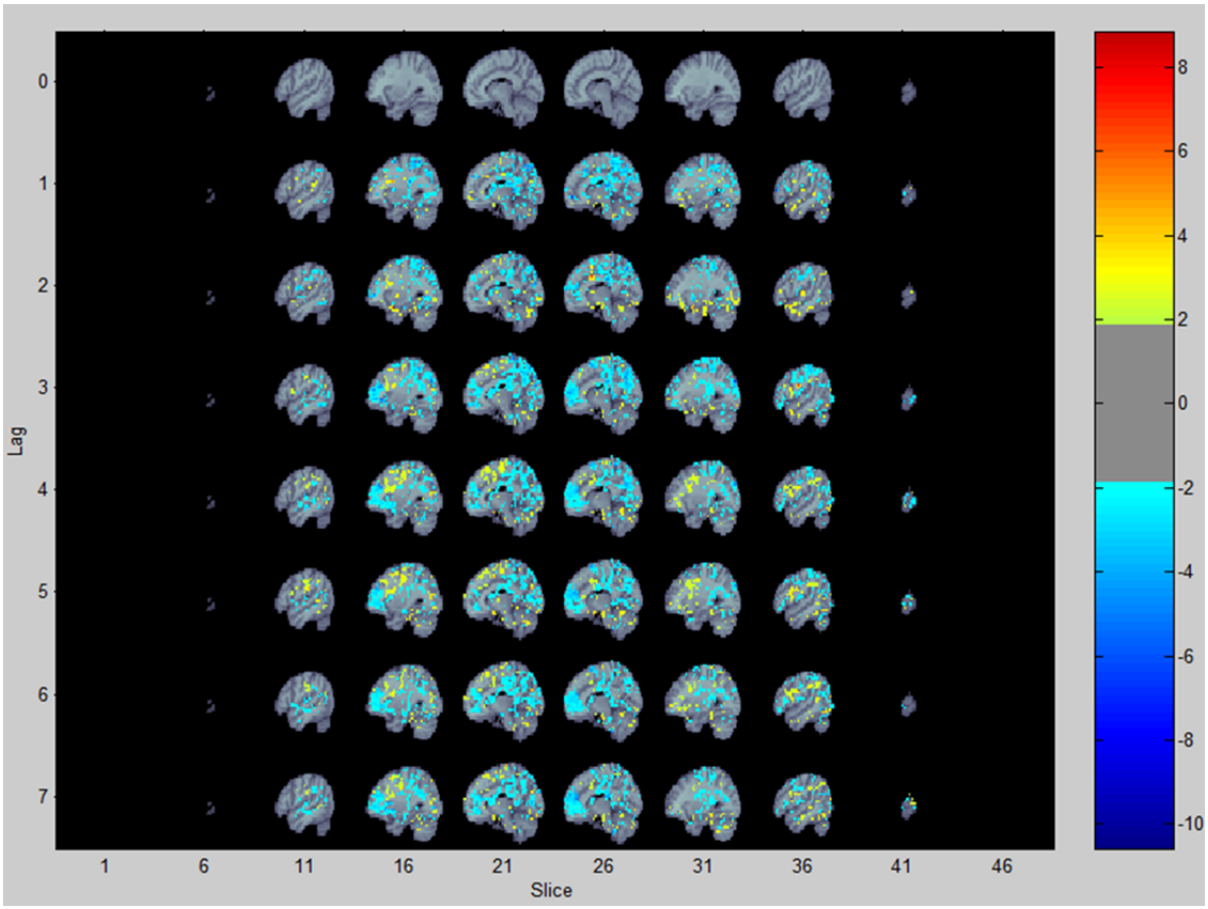

Figure B.10. Activation Map Displaying Regions Functionally Connected to the Right dlPFC in Individuals with Autism.

LV1 of seed-PLS activation map of functional connectivity with the right dlPFC for individuals with autism. Regions in hot colors represent regions comprising the positive salience neural network, while regions in the cool colors represent regions associated with the negative salience neural network. Lag refers to TRs post stimulus (TR = 1.5 seconds, lag range between 0 seconds and 10.5 seconds post-stimulus).

REFERENCES

American Psychiatric Association. 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Centers for Disease Control, 2009. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ 58, 1-20.

Adolphs, R., 2001. The neurobiology of social cognition. Curr Opin Neurobiol 11, 231-239.

Adolphs, R., 2010. What does the amygdala contribute to social cognition? Ann N Y Acad Sci 1191, 42-61.

Adolphs, R., Baron-Cohen, S., Tranel, D., 2002. Impaired recognition of social emotions following amygdala damage. J Cogn Neurosci 14, 1264-1274.

Adolphs, R., Sears, L., Piven, J., 2001. Abnormal processing of social information from faces in autism. J Cogn Neurosci 13, 232-240.

Adolphs, R., Tranel, D., Hamann, S., Young, A.W., Calder, A.J., Phelps, E.A., Anderson, A., Lee, G.P., Damasio, A.R., 1999. Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 37, 1111-1117.

Allen, D.N., Barchard, K.A., 2009. Identification of a social cognition construct for the WAIS-III. Appl Neuropsychol 16, 262-274.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2004. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8, 170-177.

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O'Riordan, M., Bullmore, E.T., 2007. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. Neuropsychologia 45, 2-14.

Bachevalier, J., Loveland, K.A., 2006. The orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism. Neurosci Biobehav Rev 30, 97-117.

Banich, M.T., Mackiewicz, K.L., Depue, B.E., Whitmer, A.J., Miller, G.A., Heller, W., 2009. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. Neurosci Biobehav Rev 33, 613-630.

Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci 2, 303-312.

Barbas, H., 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull 52, 319-330.

Barbas, H., 2007. Flow of information for emotions through temporal and orbitofrontal pathways. J Anat 211, 237-249.

Barbas, H., Zikopoulos, B., Timbie, C., 2010. Sensory Pathways and Emotional Context for Action in Primate Prefrontal Cortex. Biol Psychiatry.

Barber, A.D., Carter, C.S., 2005. Cognitive control involved in overcoming prepotent response tendencies and switching between tasks. Cereb Cortex 15, 899-912.

Baron-Cohen, S., Baldwin, D.A., Crowson, M., 1997. Do children with autism use the speaker's direction of gaze strategy to crack the code of language? Child Dev 68, 48-57.

Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C., 2000. The amygdala theory of autism. Neurosci Biobehav Rev 24, 355-364.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C., 1999. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 11, 1891-1898.

Beckmann, C.F., Jenkinson, M., Smith, S.M., 2003. General multilevel linear modeling for group analysis in FMRI. Neuroimage 20, 1052-1063.

Beer, J.S., John, O.P., Scabini, D., Knight, R.T., 2006a. Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. J Cogn Neurosci 18, 871-879.

Beer, J.S., Knight, R.T., D'Esposito, M., 2006b. Controlling the integration of emotion and cognition: the role of frontal cortex in distinguishing helpful from hurtful emotional information. Psychol Sci 17, 448-453.

Belmonte, M.K., Yurgelun-Todd, D.A., 2003. Functional anatomy of impaired selective attention and compensatory processing in autism. Brain Res Cogn Brain Res 17, 651-664.

Bennetto, L., Pennington, B.F., Rogers, S.J., 1996. Intact and impaired memory functions in autism. Child Dev 67, 1816-1835.

Berger, H.J., van Spaendonck, K.P., Horstink, M.W., Buytenhuijs, E.L., Lammers, P.W., Cools, A.R., 1993. Cognitive shifting as a predictor of progress in social understanding in high-functioning adolescents with autism: a prospective study. J Autism Dev Disord 23, 341-359.

Bird, G., Catmur, C., Silani, G., Frith, C., Frith, U., 2006. Attention does not modulate neural responses to social stimuli in autism spectrum disorders. Neuroimage 31, 1614-1624.

Blair, K.S., Smith, B.W., Mitchell, D.G., Morton, J., Vythilingam, M., Pessoa, L., Fridberg, D., Zametkin, A., Sturman, D., Nelson, E.E., Drevets, W.C., Pine, D.S., Martin, A., Blair, R.J., 2007. Modulation of emotion by cognition and cognition by emotion. Neuroimage 35, 430-440.

Bledowski, C., Prvulovic, D., Goebel, R., Zanella, F.E., Linden, D.E., 2004. Attentional systems in target and distractor processing: a combined ERP and fMRI study. Neuroimage 22, 530-540.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol Rev 108, 624-652.

Brazdil, M., Mikl, M., Marecek, R., Krupa, P., Rektor, I., 2007. Effective connectivity in target stimulus processing: a dynamic causal modeling study of visual oddball task. Neuroimage 35, 827-835.

Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 14, 277-290.

Burack, J.A., 1994. Selective attention deficits in persons with autism: preliminary evidence of an inefficient attentional lens. J Abnorm Psychol 103, 535-543.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4, 215-222.

Caplan, J.B., McIntosh, A.R., De Rosa, E., 2007. Two distinct functional networks for successful resolution of proactive interference. Cereb Cortex 17, 1650-1663.

Carter, C.S., Botvinick, M.M., Cohen, J.D., 1999. The contribution of the anterior cingulate cortex to executive processes in cognition. Rev Neurosci 10, 49-57.

Casey, B.J., 2005. Frontostriatal and frontocerebellar circuitry underlying cognitive control. In: Mayr, U., Awh, E., Keele, S.W. (Eds.), Developing individuality in the human brain: A tribute to Michael I. Posner. American Psychological Association, Washington, DC, pp. 141-166.

Casey, B.J., Tottenham, N., Fossella, J., 2002. Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. Dev Psychobiol 40, 237-254.

Choi, H.J., Zilles, K., Mohlberg, H., Schleicher, A., Fink, G.R., Armstrong, E., Amunts, K., 2006. Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. J Comp Neurol 495, 53-69.

Ciesielski, K.T., Courchesne, E., Elmasian, R., 1990. Effects of focused selective attention tasks on event-related potentials in autistic and normal individuals. Electroencephalogr Clin Neurophysiol 75, 207-220.

Ciesielski, K.T., Knight, J.E., Prince, R.J., Harris, R.J., Handmaker, S.D., 1995. Event-related potentials in cross-modal divided attention in autism. Neuropsychologia 33, 225-246.

Clark, V.P., Fannon, S., Lai, S., Benson, R., Bauer, L., 2000. Responses to rare visual target and distractor stimuli using event-related fMRI. J Neurophysiol 83, 3133-3139.

Cohen, J.D., Barch, D.M., Carter, C., Servan-Schreiber, D., 1999. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. J Abnorm Psychol 108, 120-133.

Cohen Kadosh, K., Walsh, V., Cohen Kadosh, R., 2010. Investigating face-property specific processing in the right OFA. Soc Cogn Affect Neurosci.

Conturo, T.E., Williams, D.L., Smith, C.D., Gultepe, E., Akbudak, E., Minshew, N.J., 2008. Neuronal fiber pathway abnormalities in autism: an initial MRI diffusion tensor tracking study of hippocampo-fusiform and amygdalo-fusiform pathways. J Int Neuropsychol Soc 14, 933-946.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3, 201-215.

Courchesne, E., Kilman, B.A., Galambos, R., Lincoln, A.J., 1984. Autism: processing of novel auditory information assessed by event-related brain potentials. Electroencephalogr Clin Neurophysiol 59, 238-248.

Courchesne, E., Lincoln, A.J., Kilman, B.A., Galambos, R., 1985. Event-related brain potential correlates of the processing of novel visual and auditory information in autism. J Autism Dev Disord 15, 55-76.

Courchesne, E., Lincoln, A.J., Yeung-Courchesne, R., Elmasian, R., Grillon, C., 1989. Pathophysiologic findings in nonretarded autism and receptive developmental language disorder. J Autism Dev Disord 19, 1-17.

Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., Van Amelsvoort, T., Robertson, D.M., Rowe, A., Phillips, M., McAlonan, G., Howlin, P., Murphy, D.G., 2000. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 123 (Pt 11), 2203-2212.

Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., Alexander, A.L., Davidson, R.J., 2005. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci 8, 519-526.

Damasio, A.R., Maurer, R.G., 1978. A neurological model for childhood autism. Arch Neurol 35, 777-786.

Davis, K.D., Taylor, K.S., Hutchison, W.D., Dostrovsky, J.O., McAndrews, M.P., Richter, E.O., Lozano, A.M., 2005. Human anterior cingulate cortex neurons encode cognitive and emotional demands. J Neurosci 25, 8402-8406.

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., Liaw, J., 2004a. Early social attention impairments in autism: social orienting, joint attention, and attention to distress. Dev Psychol 40, 271-283.

Dawson, G., Webb, S.J., Carver, L., Panagiotides, H., McPartland, J., 2004b. Young children with autism show atypical brain responses to fearful versus neutral facial expressions of emotion. Dev Sci 7, 340-359.

Dawson, G., Webb, S.J., McPartland, J., 2005. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Dev Neuropsychol 27, 403-424.

de Jong, M.C., van Engeland, H., Kemner, C., 2008. Attentional effects of gaze shifts are influenced by emotion and spatial frequency, but not in autism. J Am Acad Child Adolesc Psychiatry 47, 443-454.

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu Rev Neurosci 18, 193-222.

Dichter, G.S., Belger, A., 2007. Social stimuli interfere with cognitive control in autism. Neuroimage 35, 1219-1230.

Dichter, G.S., Felder, J.N., Bodfish, J.W., 2009a. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. Soc Cogn Affect Neurosci 4, 215-226.

Dichter, G.S., Felder, J.N., Bodfish, J.W., Sikich, L., Belger, A., 2009b. Mapping social target detection with functional magnetic resonance imaging. Soc Cogn Affect Neurosci 4, 59-69.

Dolcos, F., Diaz-Granados, P., Wang, L., McCarthy, G., 2008. Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. Neuropsychologia 46, 326-335.

Dolcos, F., Kragel, P., Wang, L., McCarthy, G., 2006. Role of the inferior frontal cortex in coping with distracting emotions. Neuroreport 17, 1591-1594.

Dolcos, F., McCarthy, G., 2006. Brain systems mediating cognitive interference by emotional distraction. J Neurosci 26, 2072-2079.

Donchin, E., 1981. Presidential address, 1980. Surprise!...Surprise? Psychophysiology 18, 493-513.

Donchin, E., Coles, M.G.H., 1988. Is the P300 component a manifestation of context updating? Behav Brain Sci 11, 374-375.

Donchin, E., Coles, M.G.H., 1998. Context updating and the P300. Behav Brain Sci 21, 149-168.

Eigsti, I.M., Shapiro, T., 2003. A systems neuroscience approach to autism: biological, cognitive, and clinical perspectives. Ment Retard Dev Disabil Res Rev 9, 205-215.

Elliott, R., 2003. Executive functions and their disorders. Br Med Bull 65, 49-59.

Emery, N.J., 2000. The eyes have it: the neuroethology, function and evolution of social gaze. Neurosci Biobehav Rev 24, 581-604.

Engell, A.D., Nummenmaa, L., Oosterhof, N.N., Henson, R.N., Haxby, J.V., Calder, A.J., 2010. Differential activation of frontoparietal attention networks by social and symbolic spatial cues. Soc Cogn Affect Neurosci.

Etkin, A., Egner, T., Kalisch, R., 2010. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51, 871-882.

Farroni, T., Csibra, G., Simion, F., Johnson, M.H., 2002. Eye contact detection in humans from birth. Proc Natl Acad Sci U S A 99, 9602-9605.

Farroni, T., Johnson, M.H., Csibra, G., 2004. Mechanisms of eye gaze perception during infancy. J Cogn Neurosci 16, 1320-1326.

Farroni, T., Massaccesi, S., Menon, E., Johnson, M.H., 2007. Direct gaze modulates face recognition in young infants. Cognition 102, 396-404.

Fichtenholtz, H.M., Dean, H.L., Dillon, D.G., Yamasaki, H., McCarthy, G., LaBar, K.S., 2004. Emotion-attention network interactions during a visual oddball task. Brain Res Cogn Brain Res 20, 67-80.

Garavan, H., Ross, T.J., Murphy, K., Roche, R.A., Stein, E.A., 2002. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 17, 1820-1829.

Gauthier, I., Skudlarski, P., Gore, J.C., Anderson, A.W., 2000. Expertise for cars and birds recruits brain areas involved in face recognition. Nat Neurosci 3, 191-197.

George, N., Conty, L., 2008. Facing the gaze of others. Neurophysiol Clin 38, 197-207.

Geschwind, D.H., Levitt, P., 2007. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol 17, 103-111.

Geurts, H.M., Begeer, S., Stockmann, L., 2009. Brief report: inhibitory control of socially relevant stimuli in children with high functioning autism. J Autism Dev Disord 39, 1603-1607.

Goghari, V.M., MacDonald, A.W., 3rd, 2009. The neural basis of cognitive control: response selection and inhibition. Brain Cogn 71, 72-83.

Goldstein, B., Obrzut, J.E., John, C., Ledakis, G., Armstrong, C.L., 2004. The impact of frontal and non-frontal brain tumor lesions on Wisconsin Card Sorting Test performance. Brain Cogn 54, 110-116.

Goldstein, G., Allen, D.N., Minshew, N.J., Williams, D.L., Volkmar, F., Klin, A., Schultz, R.T., 2008. The structure of intelligence in children and adults with high functioning autism. Neuropsychology 22, 301-312.

Gomot, M., Belmonte, M.K., Bullmore, E.T., Bernard, F.A., Baron-Cohen, S., 2008. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. Brain 131, 2479-2488.

Graham, R., Devinsky, O., Labar, K.S., 2007. Quantifying deficits in the perception of fear and anger in morphed facial expressions after bilateral amygdala damage. Neuropsychologia 45, 42-54.

Gray, J.R., 2001. Emotional modulation of cognitive control: approach-withdrawal states double-dissociate spatial from verbal two-back task performance. J Exp Psychol Gen 130, 436-452.

Gray, J.R., Braver, T.S., Raichle, M.E., 2002. Integration of emotion and cognition in the lateral prefrontal cortex. Proc Natl Acad Sci U S A 99, 4115-4120.

Hadjikhani, N., Joseph, R.M., Snyder, J., Chabris, C.F., Clark, J., Steele, S., McGrath, L., Vangel, M., Aharon, I., Feczko, E., Harris, G.J., Tager-Flusberg, H., 2004. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. Neuroimage 22, 1141-1150.

Hadjikhani, N., Joseph, R.M., Snyder, J., Tager-Flusberg, H., 2007. Abnormal activation of the social brain during face perception in autism. Hum Brain Mapp 28, 441-449.

Hietanen, J.K., Leppanen, J.M., Peltola, M.J., Linna-Aho, K., Ruuhiala, H.J., 2008. Seeing direct and averted gaze activates the approach-avoidance motivational brain systems. Neuropsychologia 46, 2423-2430.

Hill, E.L., 2004a. Evaluating the theory of executive dysfunction in autism. Developmental Review 24, 189.

Hill, E.L., 2004b. Executive dysfunction in autism. Trends Cogn Sci 8, 26-32.

Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat Neurosci 3, 284-291.

Hubl, D., Bolte, S., Feineis-Matthews, S., Lanfermann, H., Federspiel, A., Strik, W., Poustka, F., Dierks, T., 2003. Functional imbalance of visual pathways indicates alternative face processing strategies in autism. Neurology 61, 1232-1237.

Huettel, S.A., McCarthy, G., 2004. What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy. Neuropsychologia 42, 379-386.

Hughes, C., Russell, J., Robbins, T.W., 1994. Evidence for executive dysfunction in autism. Neuropsychologia 32, 477-492.

Huster, R.J., Westerhausen, R., Pantev, C., Konrad, C., 2010. The role of the cingulate cortex as neural generator of the N200 and P300 in a tactile response inhibition task. Hum Brain Mapp 31, 1260-1271.

Itier, R.J., Batty, M., 2009. Neural bases of eye and gaze processing: the core of social cognition. Neurosci Biobehav Rev 33, 843-863.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825-841.

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med Image Anal 5, 143-156.

Jeste, S.S., 2011. The neurology of autism spectrum disorders. Curr Opin Neurol.

Johnson, M.H., 2005. Subcortical face processing. Nat Rev Neurosci 6, 766-774.

Jones, T.B., Bandettini, P.A., Kenworthy, L., Case, L.K., Milleville, S.C., Martin, A., Birn, R.M., 2010. Sources of group differences in functional connectivity: an investigation applied to autism spectrum disorder. Neuroimage 49, 401-414.

Jones, W., Carr, K., Klin, A., 2008. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. Arch Gen Psychiatry 65, 946-954.

Joseph, R.M., Ehrman, K., McNally, R., Keehn, B., 2008. Affective response to eye contact and face recognition ability in children with ASD. J Int Neuropsychol Soc 14, 947-955.

Joseph, R.M., Tager-Flusberg, H., 2004. The relationship of theory of mind and executive functions to symptom type and severity in children with autism. Dev Psychopathol 16, 137-155.

Jou, R.J., Minshew, N.J., Keshavan, M.S., Vitale, M.P., Hardan, A.Y., 2010. Enlarged Right Superior Temporal Gyrus in Children and Adolescents with Autism. Brain Res.

Jurado, M.B., Rosselli, M., 2007. The Elusive Nature of Executive Functions: A Review of our Current Understanding. Neuropsychol Rev 17, 213-233.

Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K., Minshew, N.J., 2007. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex 17, 951-961.

Just, M.A., Cherkassky, V.L., Keller, T.A., Minshew, N.J., 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain 127, 1811-1821.

Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J., Just, M.A., 2006. Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. Brain 129, 2484-2493.

Kana, R.K., Keller, T.A., Minshew, N.J., Just, M.A., 2007. Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. Biol Psychiatry 62, 198-206.

Kanner, L., 1943. Autistic Disturbances of Affective Contact. Nervous Child 2, 217-250.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17, 4302-4311.

Kanwisher, N., Wojciulik, E., 2000. Visual attention: insights from brain imaging. Nat Rev Neurosci 1, 91-100.

Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. Annu Rev Neurosci 23, 315-341.

Kemner, C., van der Gaag, R.J., Verbaten, M., van Engeland, H., 1999. ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46, 781-789.

Kemner, C., van der Geest, J.N., Verbaten, M.N., van Engeland, H., 2004. In search of neurophysiological markers of pervasive developmental disorders: smooth pursuit eye movements? J Neural Transm 111, 1617-1626.

Kemner, C., Verbaten, M.N., Cuperus, J.M., Camfferman, G., Van Engeland, H., 1994. Visual and somatosensory event-related brain potentials in autistic children and three different control groups. Electroencephalogr Clin Neurophysiol 92, 225-237.

Kemner, C., Verbaten, M.N., Cuperus, J.M., Camfferman, G., van Engeland, H., 1995. Auditory event-related brain potentials in autistic children and three different control groups. Biol Psychiatry 38, 150-165.

Kirino, E., Belger, A., Goldman-Rakic, P., McCarthy, G., 2000. Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: an event-related functional magnetic resonance imaging study. J Neurosci 20, 6612-6618.

Klein, J.T., Shepherd, S.V., Platt, M.L., 2009. Social attention and the brain. Curr Biol 19, R958-962.

Kleinhans, N.M., Johnson, L.C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., Aylward, E., 2009. Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. Am J Psychiatry 166, 467-475.

Kleinhans, N.M., Richards, T., Sterling, L., Stegbauer, K.C., Mahurin, R., Johnson, L.C., Greenson, J., Dawson, G., Aylward, E., 2008. Abnormal functional connectivity in autism spectrum disorders during face processing. Brain 131, 1000-1012.

Kleinhans, N.M., Richards, T., Weaver, K., Johnson, L.C., Greenson, J., Dawson, G., Aylward, E., 2010. Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. Neuropsychologia 48, 3665-3670.

Kliemann, D., Dziobek, I., Hatri, A., Steimke, R., Heekeren, H.R., 2010. Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. J Neurosci 30, 12281-12287.

Klin, A., Jones, W., 2008. Altered face scanning and impaired recognition of biological motion in a 15-month-old infant with autism. Dev Sci 11, 40-46.

Klin, A., Jones, W., Schultz, R., Volkmar, F., Cohen, D., 2002. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry 59, 809-816.

Klin, A., Lin, D.J., Gorrindo, P., Ramsay, G., Jones, W., 2009. Two-year-olds with autism orient to non-social contingencies rather than biological motion. Nature 459, 257-261.

Kylliainen, A., Hietanen, J.K., 2006. Skin conductance responses to another person's gaze in children with autism. J Autism Dev Disord 36, 517-525.

LaBar, K.S., Gitelman, D.R., Mesulam, M.M., Parrish, T.B., 2001. Impact of signal-to-noise on functional MRI of the human amygdala. Neuroreport 12, 3461-3464.

Lavie, N., 1995. Perceptual load as a necessary condition for selective attention. J Exp Psychol Hum Percept Perform 21, 451-468.

Lopez, B.R., Lincoln, A.J., Ozonoff, S., Lai, Z., 2005. Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. J Autism Dev Disord 35, 445-460.

Lord, C., Risi, S., Lambrecht, L., Cook, E.H., Jr., Leventhal, B.L., DiLavore, P.C., Pickles, A., Rutter, M., 2000. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30, 205-223.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E., 1989. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. J Autism Dev Disord 19, 185-212.

Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24, 659-685.

Lorsbach, T.C., Reimer, J.F., 2008. Context processing and cognitive control in children and young adults. J Genet Psychol 169, 34-50.

MacDonald, A.W., 3rd, Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835-1838.

Macrae, C.N., Hood, B.M., Milne, A.B., Rowe, A.C., Mason, M.F., 2002. Are you looking at me? Eye gaze and person perception. Psychol Sci 13, 460-464.

Marois, R., Chun, M.M., Gore, J.C., 2004. A common parieto-frontal network is recruited under both low visibility and high perceptual interference conditions. J Neurophysiol 92, 2985-2992.

McCarthy, G., Donchin, E., 1976. The effects of temporal and event uncertainty in determining the waveforms of the auditory event related potential (ERP). Psychophysiology 13, 581-590.

McCarthy, G., Luby, M., Gore, J., Goldman-Rakic, P., 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. J Neurophysiol 77, 1630-1634.

McEvoy, R.E., Rogers, S.J., Pennington, B.F., 1993. Executive function and social communication deficits in young autistic children. J Child Psychol Psychiatry 34, 563-578.

McFie, J., Thompson, J.A., 1972. Picture arrangement: a measure of frontal lobe function? Br J Psychiatry 121, 547-552.

McIntosh, A.R., Chau, W.K., Protzner, A.B., 2004. Spatiotemporal analysis of event-related fMRI data using partial least squares. Neuroimage 23, 764-775.

McIntosh, A.R., Lobaugh, N.J., 2004. Partial least squares analysis of neuroimaging data: applications and advances. Neuroimage 23 Suppl 1, S250-263.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J.D., Gross, J.J., Ochsner, K.N., 2010. The Neural Bases of Distraction and Reappraisal. J Cogn Neurosci.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 214, 655-667.

Mevorach, C., Hodsoll, J., Allen, H., Shalev, L., Humphreys, G., 2010. Ignoring the elephant in the room: a neural circuit to downregulate salience. J Neurosci 30, 6072-6079.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24, 167-202.

Mitchell, D.G., Nakic, M., Fridberg, D., Kamel, N., Pine, D.S., Blair, R.J., 2007. The impact of processing load on emotion. Neuroimage 34, 1299-1309.

Nacewicz, B.M., Dalton, K.M., Johnstone, T., Long, M.T., McAuliff, E.M., Oakes, T.R., Alexander, A.L., Davidson, R.J., 2006. Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. Arch Gen Psychiatry 63, 1417-1428.

Neumann, D., Spezio, M.L., Piven, J., Adolphs, R., 2006. Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. Soc Cogn Affect Neurosci 1, 194-202.

Norris, C.J., Chen, E.E., Zhu, D.C., Small, S.L., Cacioppo, J.T., 2004. The interaction of social and emotional processes in the brain. J Cogn Neurosci 16, 1818-1829.

Noudoost, B., Chang, M.H., Steinmetz, N.A., Moore, T., 2010. Top-down control of visual attention. Curr Opin Neurobiol 20, 183-190.

Ochsner, K.N., 2008. The social-emotional processing stream: five core constructs and their translational potential for schizophrenia and beyond. Biol Psychiatry 64, 48-61.

Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. Trends Cogn Sci 9, 242-249.

Ochsner, K.N., Phelps, E., 2007. Emerging perspectives on emotion-cognition interactions. Trends Cogn Sci 11, 317-318.

Owen, A.M., Roberts, A.C., Hodges, J.R., Summers, B.A., Polkey, C.E., Robbins, T.W., 1993. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain 116 (Pt 5), 1159-1175.

Ozonoff, S., 1995. Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. Neuropsychology 9, 491-500.

Ozonoff, S., Pennington, B.F., Rogers, S.J., 1991. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J Child Psychol Psychiatry 32, 1081-1105.

Ozonoff, S., Strayer, D.L., McMahon, W.M., Filloux, F., 1994. Executive function abilities in autism and Tourette syndrome: an information processing approach. J Child Psychol Psychiatry 35, 1015-1032.

Pascualvaca, D.M., Fantie, B.D., Papageorgiou, M., Mirsky, A.F., 1998. Attentional capacities in children with autism: is there a general deficit in shifting focus? J Autism Dev Disord 28, 467-478.

Pasley, B.N., Mayes, L.C., Schultz, R.T., 2004. Subcortical discrimination of unperceived objects during binocular rivalry. Neuron 42, 163-172.

Paxton, J.L., Barch, D.M., Racine, C.A., Braver, T.S., 2008. Cognitive control, goal maintenance, and prefrontal function in healthy aging. Cereb Cortex 18, 1010-1028.

Pellicano, E., 2007. Links between theory of mind and executive function in young children with autism: clues to developmental primacy. Dev Psychol 43, 974-990.

Pelphrey, K.A., Carter, E.J., 2008a. Brain mechanisms for social perception: lessons from autism and typical development. Ann N Y Acad Sci 1145, 283-299.

Pelphrey, K.A., Carter, E.J., 2008b. Charting the typical and atypical development of the social brain. Dev Psychopathol 20, 1081-1102.

Pelphrey, K.A., Mitchell, T.V., McKeown, M.J., Goldstein, J., Allison, T., McCarthy, G., 2003. Brain activity evoked by the perception of human walking: controlling for meaningful coherent motion. J Neurosci 23, 6819-6825.

Pelphrey, K.A., Morris, J.P., McCarthy, G., 2005. Neural basis of eye gaze processing deficits in autism. Brain 128, 1038-1048.

Pelphrey, K.A., Morris, J.P., McCarthy, G., Labar, K.S., 2007. Perception of dynamic changes in facial affect and identity in autism. Soc Cogn Affect Neurosci 2, 140-149.

Pelphrey, K.A., Sasson, N.J., Reznick, J.S., Paul, G., Goldman, B.D., Piven, J., 2002. Visual scanning of faces in autism. J Autism Dev Disord 32, 249-261.

Pelphrey, K.A., Viola, R.J., McCarthy, G., 2004. When strangers pass: processing of mutual and averted social gaze in the superior temporal sulcus. Psychol Sci 15, 598-603.

Pennington, B.F., Ozonoff, S., 1996. Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37, 51-87.

Pessoa, L., 2008. On the relationship between emotion and cognition. Nat Rev Neurosci 9, 148-158.

Pessoa, L., 2010. Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". Neuropsychologia 48, 3416-3429.

Pessoa, L., Adolphs, R., 2010. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci 11, 773-783.

Pessoa, L., Kastner, S., Ungerleider, L.G., 2002a. Attentional control of the processing of neutral and emotional stimuli. Brain Res Cogn Brain Res 15, 31-45.

Pessoa, L., McKenna, M., Gutierrez, E., Ungerleider, L.G., 2002b. Neural processing of emotional faces requires attention. Proc Natl Acad Sci U S A 99, 11458-11463.

Pierce, K., Muller, R.A., Ambrose, J., Allen, G., Courchesne, E., 2001. Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. Brain 124, 2059-2073.

Piven, J., Palmer, P., 1999. Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. Am J Psychiatry 156, 557-563.

Posner, M.I., Petersen, S.E., 1990. The attention system of the human brain. Annu Rev Neurosci 13, 25-42.

Prior, M., Hoffmann, W., 1990. Brief report: neuropsychological testing of autistic children through an exploration with frontal lobe tests. J Autism Dev Disord 20, 581-590.

Pritchard, W.S., Raz, N., August, G.J., 1987. Visual augmenting/reducing and P300 in autistic children. J Autism Dev Disord 17, 231-242.

Remington, A., Swettenham, J., Campbell, R., Coleman, M., 2009. Selective attention and perceptual load in autism spectrum disorder. Psychol Sci 20, 1388-1393.

Riby, D.M., Hancock, P.J., 2009. Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. J Autism Dev Disord 39, 421-431.

Ridderinkhof, K.R., van den Wildenberg, W.P., Segalowitz, S.J., Carter, C.S., 2004. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cogn 56, 129-140.

Rinehart, N.J., Bradshaw, J.L., Brereton, A.V., Tonge, B.J., 2002. A clinical and neurobehavioural review of high-functioning autism and Asperger's disorder. Aust N Z J Psychiatry 36, 762-770.

Rogers, B.P., Morgan, V.L., Newton, A.T., Gore, J.C., 2007. Assessing functional connectivity in the human brain by fMRI. Magn Reson Imaging 25, 1347-1357.

Rougier, N.P., Noelle, D.C., Braver, T.S., Cohen, J.D., O'Reilly, R.C., 2005. Prefrontal cortex and flexible cognitive control: rules without symbols. Proc Natl Acad Sci U S A 102, 7338-7343.

Rowe, J.B., 2010. Connectivity Analysis is Essential to Understand Neurological Disorders. Front Syst Neurosci 4.

Rumsey, J.M., 1985. Conceptual problem-solving in highly verbal, nonretarded autistic men. J Autism Dev Disord 15, 23-36.

Rumsey, J.M., Hamburger, S.D., 1988. Neuropsychological findings in high-functioning men with infantile autism, residual state. J Clin Exp Neuropsychol 10, 201-221.

Russo, N., Flanagan, T., Iarocci, G., Berringer, D., Zelazo, P.D., Burack, J.A., 2007. Deconstructing executive deficits among persons with autism: implications for cognitive neuroscience. Brain Cogn 65, 77-86.

Sasson, N.J., Pinkham, A.E., Carpenter, K.L.H., Belger, A., in press. The Benefit of Directly Comparing Autism and Schizophrenia to Reveal Mechanisms of Social Cognitive Impairment. . J Neurodev Disord.

Scheperjans, F., Hermann, K., Eickhoff, S.B., Amunts, K., Schleicher, A., Zilles, K., 2008. Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb Cortex 18, 846-867.

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., Murphy, D.G., 2006. Neural correlates of executive function in autistic spectrum disorders. Biol Psychiatry 59, 7-16.

Schultz, R., 2008. Converging Imaging Evidence for the Role of the Temporal Lobes in the Pathobiology of Autism Spectrum Disorders. *Development and Brain Systems in Autism.* 35th Carnegie Symposium on Cognition, Pittsburgh, PA.

Schultz, R.T., 2005. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int J Dev Neurosci 23, 125-141.

Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J., Gore, J.C., 2000. Abnormal ventral

temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry 57, 331-340.

Senju, A., Hasegawa, T., 2005. Direct gaze captures visuospatial attention. Visual Cognition 12, 127-144.

Senju, A., Johnson, M.H., 2009. The eye contact effect: mechanisms and development. Trends Cogn Sci 13, 127-134.

Senju, A., Yaguchi, K., Tojo, Y., Hasegawa, T., 2003. Eye contact does not facilitate detection in children with autism. Cognition 89, B43-51.

Shafritz, K.M., Dichter, G.S., Baranek, G.T., Belger, A., 2008. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. Biol Psychiatry 63, 974-980.

Shafritz, K.M., Kartheiser, P., Belger, A., 2005. Dissociation of neural systems mediating shifts in behavioral response and cognitive set. Neuroimage 25, 600-606.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp 17, 143-155.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1, S208-219.

Sokhadze, E., Baruth, J., Tasman, A., Sears, L., Mathai, G., El-Baz, A., Casanova, M.F., 2009. Event-related potential study of novelty processing abnormalities in autism. Appl Psychophysiol Biofeedback 34, 37-51.

Solomon, M., Ozonoff, S.J., Cummings, N., Carter, C.S., 2008. Cognitive control in autism spectrum disorders. Int J Dev Neurosci 26, 239-247.

Solomon, M., Ozonoff, S.J., Ursu, S., Ravizza, S., Cummings, N., Ly, S., Carter, C.S., 2009. The neural substrates of cognitive control deficits in autism spectrum disorders. Neuropsychologia 47, 2515-2526.

South, M., Ozonoff, S., McMahon, W.M., 2007. The relationship between executive functioning, central coherence, and repetitive behaviors in the high-functioning autism spectrum. Autism 11, 437-451.

Spezio, M.L., Huang, P.Y., Castelli, F., Adolphs, R., 2007. Amygdala damage impairs eye contact during conversations with real people. J Neurosci 27, 3994-3997.

Stuss, D.T., Benson, D.F., 1984. Neuropsychological studies of the frontal lobes. Psychol Bull 95, 3-28.

Stuss, D.T., Floden, D., Alexander, M.P., Levine, B., Katz, D., 2001. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia 39, 771-786.

Sutton, S., Braren, M., Zubin, J., John, E.R., 1965. Evoked-Potential Correlates of Stimulus Uncertainty. Science 150, 1187-1188.

Swettenham, J., Baron-Cohen, S., Charman, T., Cox, A., Baird, G., Drew, A., Rees, L., Wheelwright, S., 1998. The frequency and distribution of spontaneous attention shifts between social and nonsocial stimuli in autistic, typically developing, and nonautistic developmentally delayed infants. J Child Psychol Psychiatry 39, 747-753.

Townsend, J., Courchesne, E., Covington, J., Westerfield, M., Harris, N.S., Lyden, P., Lowry, T.P., Press, G.A., 1999. Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci 19, 5632-5643.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273-289.

von Grunau, M., Anston, C., 1995. The detection of gaze direction: a stare-in-the-crowd effect. Perception 24, 1297-1313.

Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J., 2001. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30, 829-841.

Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M.A., Ochsner, K.N., 2008. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron 59, 1037-1050.

Wang, L., McCarthy, G., Song, A.W., Labar, K.S., 2005. Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. Emotion 5, 12-22.

Weschler, D., 1999. Weschler Abbreviated Scale of Intelligence (WASI). Harcourt Assessment, San Antonio, TX.

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14, 1370-1386.

Yamasaki, H., LaBar, K.S., McCarthy, G., 2002. Dissociable prefrontal brain systems for attention and emotion. Proc Natl Acad Sci U S A 99, 11447-11451.

Yerys, B.E., Hepburn, S.L., Pennington, B.F., Rogers, S.J., 2007. Executive function in preschoolers with autism: evidence consistent with a secondary deficit. J Autism Dev Disord 37, 1068-1079.